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(52) UK CL (Edition O)
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U1S S2414

(56) and (58) continued overleaf

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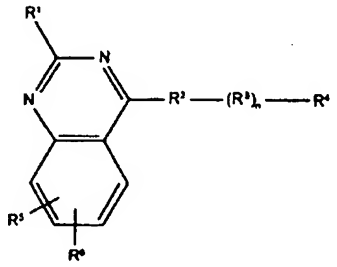
(74) continued overleaf

(54) Quinazoline antagonists of alpha 1c adrenergic receptors

(57)

(I)



wherein:
R^1 is selected from hydrogen, C_{1-6}alkyl, C_{1-6}cycloalkyl, hydroxy, C_{1-6}alkoxy, -COO(C_{1-6}alkyl), halogen, phenyl, phenylcarbonyl, substituted phenyl, pyridinyl, pyrimidinyl or pyrrolyl;
n is 0 or 1; R^3 is a C_{1-6}alkylene chain optionally mono- or disubstituted independently with hydrogen, C_{1-6}alkyl, hydroxy, C_{1-6}alkoxy, fluoro, phenyl or substituted phenyl substituents;
R^5 and R^6 are independently selected from the group consisting of hydrogen, C_{1-6}alkyl, hydroxy, C_{1-6}alkoxy or halogen; and
R^2 and R^4 are as defined in the specification; and salts thereof are useful for treating benign prostatic hyperplasia.

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(58) Field of Search
UK CL (Edition N) **C2C CNF CSF CWE CZB**
INT CL[6] **C07D**
Online:WPI

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ANTAGONISTS OF α-1C ADRENERGIC RECEPTORS

BACKGROUND OF THE INVENTION

Benign prostatic hyperplasia (BPH) is a benign neoplasm found primarily in older males, see H. Lepor, *Urologic Clinics of North America, 17,* No.3, 651-659 (1990). BPH clinical manifestations include bladder outlet obstruction resulting from enlargement of the prostate gland. The condition is most often treated by transurethral prostatectomy, see H. Lepor, *et al, The Journal of Urology, 148,* 1467-1474 (1992).

The prostate has been demonstrated to be rich in α-1 adrenergic receptors, see S. Raz, *et al , British Journal of Urology, 45,* 663-667 (1973). It has been reported that BPH can be treated with an α-1 adrenergic receptor blocker, which may act by relaxing the tension of prostate smooth muscle, thus relieving the symptoms of infravesical obstruction, see H. Lepor *et al, supra at* 1473. Recently the α-1 adrenergic receptor mRNA from human prostate has been analyzed and three subtypes have been identified: α-1B, α-1C and α-1D, with α-1C comprising 70% of the mRNA. This may account for the cardiovascular and central nervous system side effects caused by nondiscriminatory blockade of α-1 adrenergic receptor subtypes, see D.T. Price, *et al, The Journal of Urology, 150,* 546-551 (1993), PCT Application WO 94/10989. α–1 adrenergic antagonists which bind selectively to the α–1C adrenergic receptor subtype preferentially over the α–1B and α–1D subtypes have been claimed as useful in the treatment of BPH, see PCT Application WO 94/10989, *supra.* Testosterone 5α–reductase inhibitors such as Proscar™ (Merck) have been shown to be useful in the treatment of a variety of androgen responsive diseases such as BPH and prostate cancer, see Frye, *et al,* US Patent 5,302,589, PCT Application WO 94/10989, *supra.* Additionally, α-1 adrenergic receptor antagonists and dopamine D_2 antagonists in combination have

been shown to be useful as an antipsychotic treatment, see Hrib, *et al, J. Med. Chem., 37,* 2308-2314 (1994).

α1-adrenergic antagonists have also been shown to differentially control serotonin release in the hippocampus and striatum, see Rouquier, *et al,* Eur. J. *Pharmacol., 261(1-2),* 59-64 (1994), have an effect on susceptibility to malignant arrhythmias, see Billman, *J.Cardiovasc.Pharmacol.,* 24*(3),* 394-402 (1994), to possess dopamine receptor agonist activity and 5-HT receptor antagonist activity, see PCT patent application WO 9305035, to effect hyperthermia and hyperglycemia, see Nonogaki K, *et al, Eur. J. Pharmacol.,262(1-2):*177-180 (1994), to have a role in treatment of obstructive detrusor instability, see C.R.Chapple, *et al, Brit. J. of Urology, 73,* 117-123 (1994), and to have hemodynamic effects in cirrhotic patients with portal hypertension, see Albillos A, *et al, Hepatology, 20(3):* 611-617 (1994).

α1-adrenergic agonists have been shown to precondition rabbit ischemic myocardium independent of adenosine by direct activation of protein kinase, see Tsuchida, *et al, Circ. Res., 75(3):* 576-585 (1994).

Compounds which modulate α1-adrenergic subtype response have additionally been implicated as useful for treatment of conditions such as hypertension, see US Patent 4,440,769, ischemic heart disease, and psychoses, see Japanese Patent JP 03264579, congestive heart failure, see PCT application WO 92/00741, cerebral angiopathy, see Japanese Patent JP03264579, sympathetically maintained pain in peripheral tissues, see PCT application WO 92/14453 and 91/2806; allergies, hypolipemia, peripheral vascular disorders and glaucoma, see French Patent FR 2574401, thrombosis and asthma, see European Patent 62596, dysuria and pollakiuria, see Japanese Patent 03090027, bronchial spasms, hemorrhoids and nasal congestion, see South African Patent ZA 8502785.

Furthermore, α1-adrenergic subtypes have been shown to have a role in mediating adrenergic vasoconstriction in kidney of two kidney, one-clip Goldblatt and deoxycorticosterone acetate-salt hypertensive rats, see Sattar, et al, *J. Cardiovasc. Pharmacol. 24(3),* 420-428 (1994), to have analgesic potency after systemic administration in amphibians, see Brenner, *et al, J. Pharmacol. Exp. Ther., 270(2),* 540-545 (1994), to be involved in the effects of hippocampal vasopressinergic treatment on retrieval and relearning, see Metzger, *et al, Behav. Neural. Biol.,* 62(2), 90-99 (1994), to have a role in sleep-wakefulness and body temperature regulation

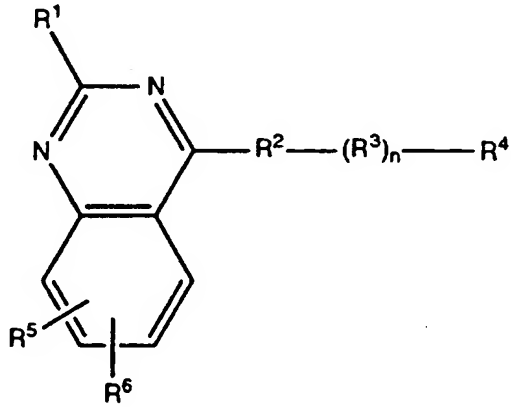
Brain Res. Bull., 35(2), 171-177 (1994), to be involved with cardiac myocytes following coronary artery constriction in rats, see Cheng, *et al, Cardiovasc. Res., 28(7),* 1070-1082 (1994), to mediate biochemical, molecular, and morphologic features of cultured myocardial cell hypertrophy, see *J. Biol. Chem., 268,* 15374 (1993), to be involved with phasic and tonic vasoconstrictor responses, see Wong P.C., *et al, Eur. J. Pharmacol;.262(1-2):*185-188 (1994), to have a role in human liver during intraabdominal sepsis, see Hwang T, *et al, Hepatology;20(3):* 638-642 (1994), to modulate phosphatidylinositol cycle in cultured rat cardiomyocytes, see Van Heugten H, *et al, J. Mol. Cell Cardiol. 26(8):*1081-1093 (1994), and to be involved in glucose release and thus diabetes, see Capusso, A., *et al, Gen. Comp. Endocrinol., 95 (3),* 457-463 (1994).

Compounds of the present invention inhibit the α-1c adrenergic receptor subtype and are therefore useful in the treatment of BPH and other obstructive conditions in which urination is difficult or strained.

SUMMARY OF THE INVENTION

Quinazoline compounds useful as antagonists of α–1C adrenoceptor of the following formula (I):

(I)



wherein:

R^1 is selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{1-6}cycloalkyl, hydroxy, C_{1-6}alkoxy, -COO(C_{1-6}alkyl), halogen, phenyl, phenylcarbonyl, substituted phenyl, pyridinyl, pyrimidinyl or pyrrolyl;

n is an integer selected from the group consisting of 0 or 1;

R^3 is a C_{1-6}alkylene chain optionally mono- or disubstituted independently with hydrogen, C_{1-6}alkyl, hydroxy, C_{1-6}alkoxy, fluoro, phenyl or substituted phenyl substituents;

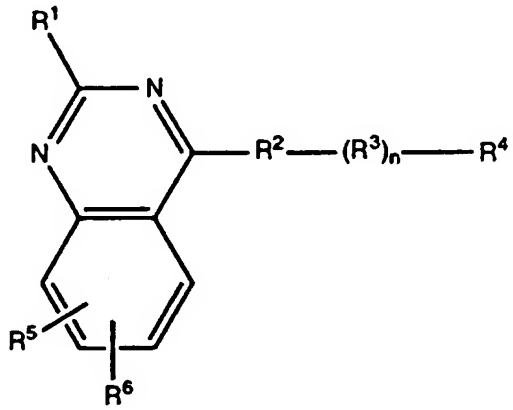
R^5 and R^6 are independently selected from the group consisting of hydrogen, C_{1-6}alkyl, hydroxy, C_{1-6}alkoxy or halogen;

R^2 and R^4 are selected from a variety of substituents.

DETAILED DESCRIPTION OF THE INVENTION

This invention relates to novel α–1C adrenoceptor binding compounds of the following formula (I):

(I)



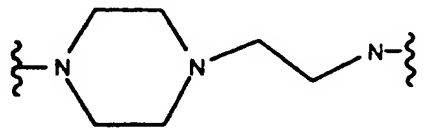
wherein:

R^1 is selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{1-6}cycloalkyl, hydroxy, C_{1-6}alkoxy, -COO(C_{1-6}alkyl), halogen, phenyl, phenylcarbonyl, substituted phenyl, pyridinyl, pyrimidinyl or pyrrolyl;

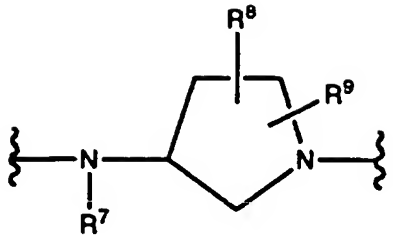
R^2 is selected from the group consisting of

(a) NH,

(b)



(c)



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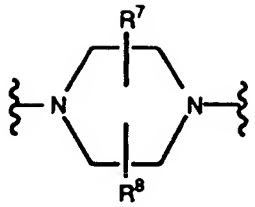

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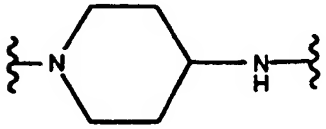

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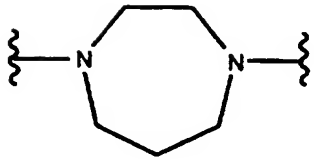

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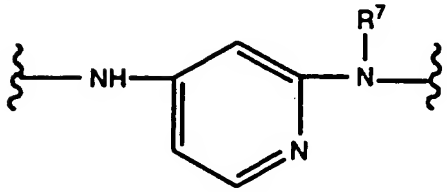

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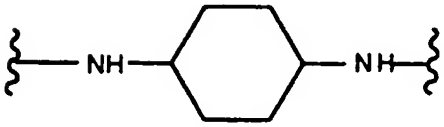
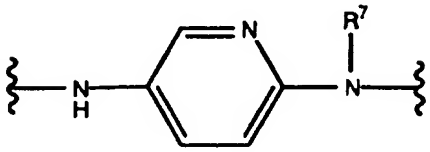
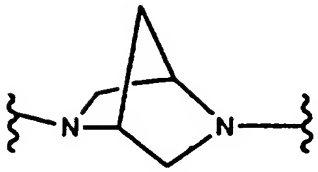


(i)



(j) $-N(CH_2)_mNR^7-$,

(k)



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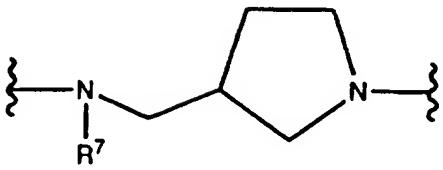
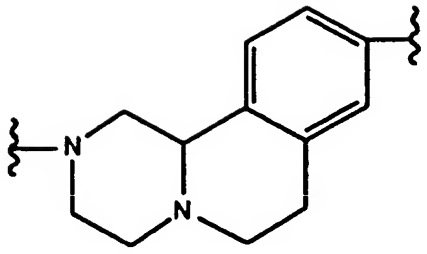
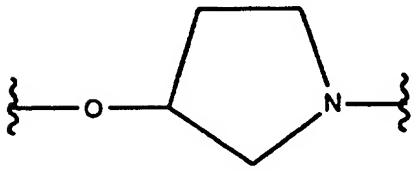


(m)



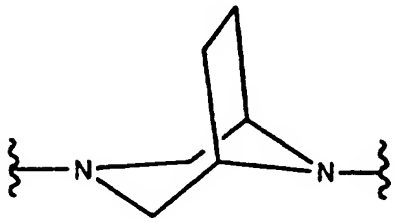
(n) $-(CH_2)_mNR^7-$,

(o)



(p) $-SO(CH_2)_mNR^7-$,

(q)



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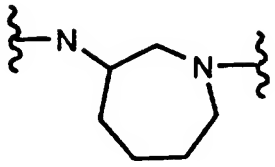

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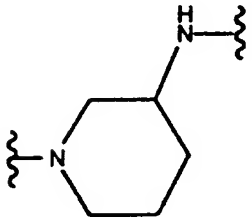

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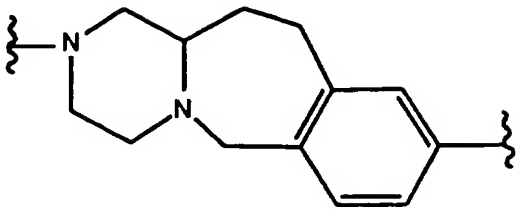

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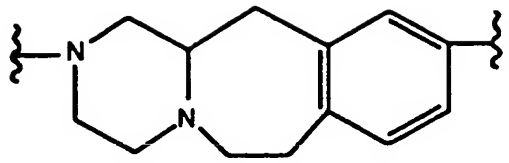

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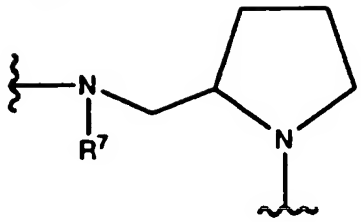

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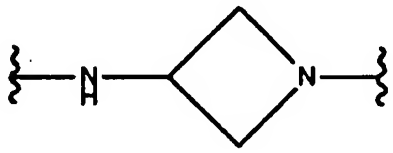

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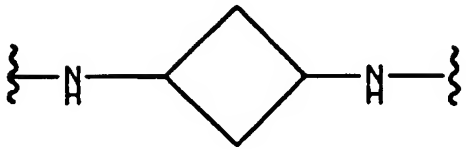

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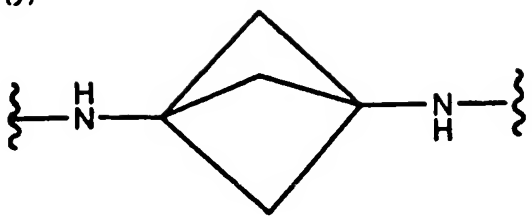

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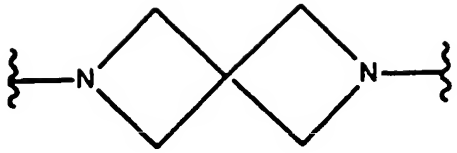

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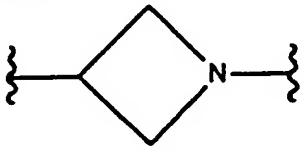

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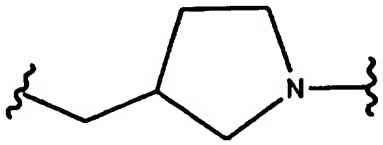

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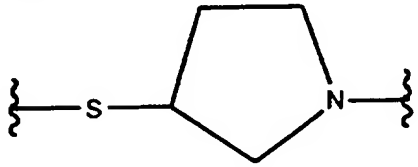

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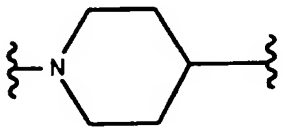

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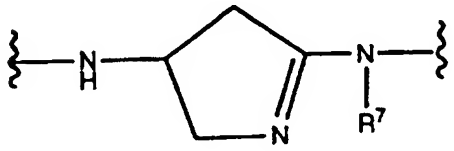

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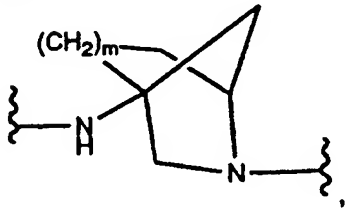

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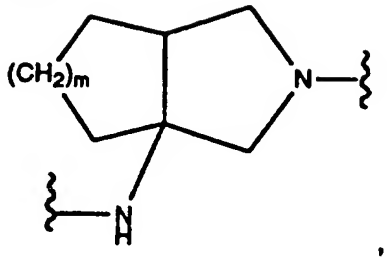

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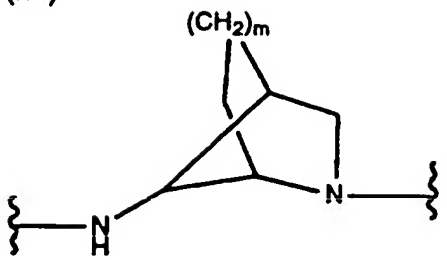

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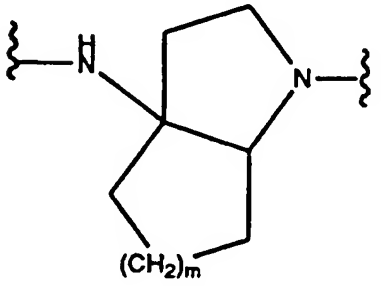

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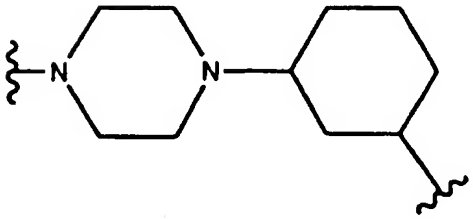

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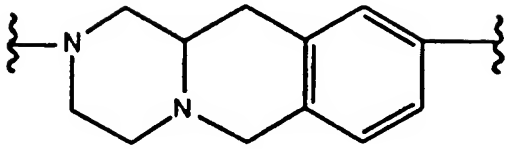

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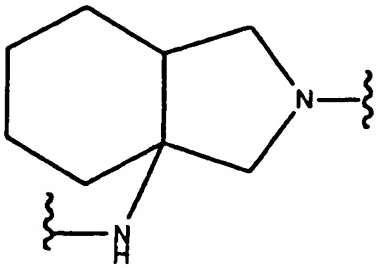

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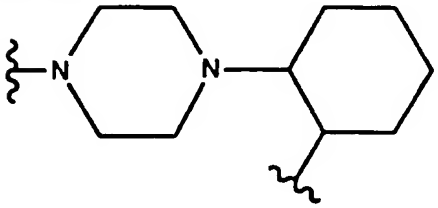

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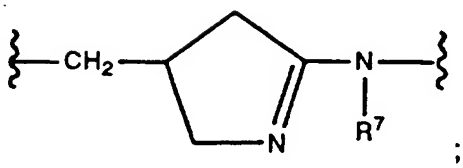


wherein:

R^7, R^8 and R^9 are selected from hydrogen, C_{1-6}alkyl, phenyl or benzyl;

m is an integer selected from the group consisting of 0, 1, 2, 3, 4, 5 or 6;

n is an integer selected from the group consisting of 0 or 1;

R^3 is a C_{1-6}alkylene chain optionally mono- or disubstituted independently with hydrogen, C_{1-6}alkyl, hydroxy, C_{1-6}alkoxy, fluoro, phenyl or substituted phenyl substituents;

R^4 is selected from the group consisting of hydrogen, amino, mono- or di(C_{1-6}alkyl)amino, phenyl, substituted phenyl, phenyloxy, (substituted phenyl)oxy, pyrrolyl, pyrrolyl mono- or disubstituted independently with C_{1-8}alkyl, -C_{1-6}alkylCOO(C_{1-4}alkyl) or C_{1-6}alkylcarbamylC_{1-6}alkyl substituents, C_{1-8}alkylcarbonylamino, 5 or 6 membered saturated heterocycle, (5 or 6 membered saturated heterocycle)carbonylamino, substituted 5 or 6 membered saturated heterocycle, (substituted 5 or 6 membered saturated heterocycle)C_{1-6}alkenyl, (substituted 5 or 6 membered saturated heterocycle)carbonyl, (substituted 5 or 6 membered saturated heterocycle)C_{1-6}alkylcarbonyl, quinoline, 9 or 10 membered heterobicycle which is partially aromatic, substituted 9 or 10 membered heterobicycle which is partially aromatic or (substituted 9 or 10 membered heterobicycle which is partially aromatic)carbonyl;

R^5 and R^6 are independently selected from the group consisting of hydrogen, C_{1-6}alkyl, hydroxy, C_{1-6}alkoxy or halogen;

substituted phenyl in more detail is phenyl mono-, di- or tri-substituted independently with C_{1-6}alkyl, C_{1-6}alkenyl, halo, nitro, amino, hydroxy, oxo, carboxy, C_{1-6}alkyl substituted with hydroxy, C_{1-6}alkoxy, C_{1-6}alkenyloxy, C_{1-6}alkenyloxyC_{1-6}alkyl, C_{1-6}alkylcarbonyl, C_{1-6}alkoxycarbonyl, C_{1-6}alkoxycarbonylamino, C_{1-6}alkoxycarbonylC_{1-6}alkoxy, biphenylcarbonylC_{1-6}alkoxy, napthylcarbonylC_{1-6}alkoxy, C_{1-6}alkoxycarbonylC_{1-6}alkyl, C_{1-6}alkoxycarbonylC_{1-6}alkylcarbonylamino, aminosulfonyl, sulfonylamino, C_{1-6}alkylsulfonylamino, C_{1-6}alkylcarbonylamino, C_{1-6}alkylaminosulfonyl, C_{1-6}alkylaminocarbonyl, aminoC_{1-6}alkylaminosulfonyl, aminosulfonylC_{1-6}alkylaminosulfonyl, C_{1-6}alkylsulfonylaminoC_{1-6}alkyl, C_{1-}

$_{6}$alkylsulfonylaminoC_{1-6}alkylaminosulfonyl, C_{3-6}cycloalkylaminosulfonyl, mono- or di(C_{1-6}alkyl)amino, mono- or di(C_{1-6}alkyl)aminosulfonyl, mono- or di(C_{1-6}alkyl)aminocarbonylC_{1-6}alkoxy, heteroarylaminosulfonyl, dioxopyrimidinylaminosulfonyl, (C_{1-6}alkylcarbonyl)(C_{1-6}alkyl)aminosulfonyl, (C_{1-6}alkoxycarbonyl)(C_{1-6}alkyl)aminosulfonyl, C_{1-6}alkylcarbonylamino, C_{1-6}alkylcarbonylaminosulfonyl, C_{1-6}alkoxycarbonylC_{1-6}alkylaminosulfonyl, C_{1-6}alkylcarbonylaminoC_{1-6}alkylaminosulfonyl, fluorinated C_{1-6}alkyl, fluorinatedC_{1-6}alkylcarbonylaminoC_{1-6}alkylaminosulfonyl, fluorinatedC_{1-6}alkylsulfonate, fluorinatedC_{1-6}alkylsulfonylaminoC_{1-6}alkylaminosulfonyl, C_{1-6}alkylaminocarbonylamino, C_{1-6}alkylaminocarbonylaminoC_{1-6}alkylaminosulfonyl, C_{1-6}alkoxycarbonylaminoC_{1-6}alkylaminosulfonyl, C_{1-6}alkylcarbonyl(C_{1-6}alkyl)aminoC_{1-6}alkyl(C_{1-6}alkyl)aminosulfonyl, C_{1-4}alkylcarbonylsulfonylaminoC_{1-6}alkylaminosulfonyl, C_{1-6}alkylaminocarbonylC_{1-6}alkyl(C_{1-6}alkyl)aminosulfonyl, fluorinatedC_{1-4}alkylcarbonylsulfonylaminoC_{1-6}alkylaminosulfonyl, C_{1-6}alkylaminocarbonylC_{1-6}alkylaminosulfonyl, (C_{1-6}alkylaminocarbonyl)(C_{1-6}alkyl)methyleneaminosulfonyl, napthylaminocarbonylC_{1-6}alkylaminosulfonyl, C_{1-6}alkylaminocarbonylC_{1-8}alkylamino, C_{1-6}alkylaminocarbonylC_{1-8}alkylaminosulfonyl, mono- or di(C_{1-6}alkyl)aminocarbonylC_{1-8}alkylaminosulfonyl, mono- or di(C_{1-6}alkyl)aminocarbonylC_{1-6}alkyl(C_{1-6}alkyl)aminosulfonyl, phenyl, phenylC_{1-6}alkyl, phenylC_{1-6}alkoxy, phenylcarbonyl, phenylcarbonylamino, phenylC_{1-6}alkylcarbonyl, phenylC_{1-6}alkylcarbonylamino, phenylC_{1-6}alkylcarbonylaminosulfonyl, phenylC_{1-6}alkylcarbonylaminoC_{1-6}alkyl, phenylaminosulfonyl, phenylsulfonylaminoC_{1-6}alkyl, phenylcarbonylC_{1-6}alkoxy, phenylC_{1-6}alkylaminocarbonylaminosulfonyl, phenylcarbonylaminoC_{1-6}alkylaminosulfonyl, phenylcarbonylsulfonylaminoC_{1-6}alkylaminosulfonyl, phenoxy, halophenoxy, halophenylcarbonylC_{1-6}alkoxy, halophenylcarbonylamino, phenylC_{1-6}alkylaminosulfonyl, phenylaminocarbonylamino, phenylaminocarbonylaminosulfonyl, phenylC_{1-6}alkylaminocarbonylaminosulfonyl, phenylcarbonylaminosulfonyl, C_{1-6}alkylphenylcarbonylaminosulfonyl, phenylC_{1-6}alkoxycarbonylC_{1-6}alkyl, thiadiazolyl, 5, 6 or 7 membered saturated heterocycle, substituted 5, 6 or 7 membered saturated heterocycle, (5, 6 or 7 membered saturated heterocycle)carbonyl, (5, 6 or 7 membered saturated heterocycle)sulfonyl, (substituted 5, 6 or 7 membered saturated heterocycle)C_{1-6}alkyl, (substituted 5, 6 or 7 membered saturated

heterocycle)carbonyl, (substituted 5, 6 or 7 membered saturated heterocycle)sulfonyl, (substituted 5, 6 or 7 membered saturated heterocycle)aminosulfonyl, heteroaryl, heteroarylaminosulfonyl, substituted heteroaryl, (substituted heteroaryl)amino sulfonyl, carbamyl, carbamylamino, carbamylC_{1-6}alkylamino, carbamylC_{1-6}alkylaminosulfonyl, (carbamyl)(phenyl)methyleneaminosulfonyl, (carbamyl)(benzyl)methyleneaminosulfonyl, (carbamyl)(C_{1-6}alkyl)methyleneaminosulfonyl, carbamylC_{1-6}alkyl(C_{1-6}alkyl)aminosulfonyl, carbamylC_{1-8}alkylaminosulfonyl, carbamylaminoC_{1-6}alkylaminosulfonyl, carbamyl(5, 6 or 7 membered saturated heterocycle), azaindolylC_{1-6}alkylaminosulfonyl, cyano or carboxyC_{1-6}alkoxy substituents;

5, 6 or 7 membered saturated heterocycle in more detail is a 5, 6 or 7 membered saturated heterocycle interrupted by 1, 2, 3, or 4 N or O heteroatoms, with the proviso that any two O atoms are not bonded to each other;

substituted 5, 6 or 7 membered saturated heterocycle in more detail is a 5, 6 or 7 membered saturated heterocycle mono-, di-, or trisubstituted independently with hydroxy, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, carbamyl, acetyl, amino, C_{1-6}alkylsulfonyl, -COO(C_{1-4}alkyl), benzyl or C_{1-6}alkylcarbonyl substituents;

9 or 10 membered heterobicycle which is partially aromatic in more detail is a heterobicycle interrupted by 1, 2, 3, or 4 N heteroatoms,

substituted 9 or 10 membered heterobicycle which is partially aromatic in more detail is a 9 or 10 membered heterobicycle mono-, di-, or trisubstituted independently with hydroxy, oxo, C_{1-6}alkyl, C_{1-6}alkoxy or amino substituents;

heteroaryl in more detail is a 5, 6 or 7 membered aromatic ring optionally interrupted by 1, 2, 3 or 4 N, S, or O heteroatoms, with the proviso that any two O or S atoms are not bonded to each other;

substituted heteroaryl in more detail is a 9 or 10 membered heterobicycle mono-, di-, or trisubstituted independently with hydroxy, oxo, C_{1-6}alkyl, C_{1-6}alkoxy or amino substituents;

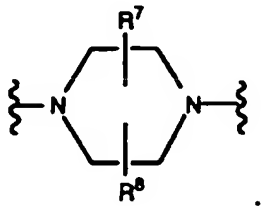
or a pharmaceutically acceptable acid-addition or base-addition salt thereof.

Particular groups of compounds of the formula (I) are the following:

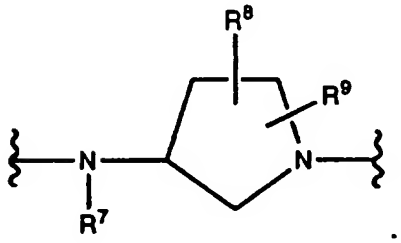
1. R^4 is phenyl disubstituted with methoxy and aminosulfonyl.

2. $R^4$is (3-aminosulfonyl-4-methoxy)phenyl.

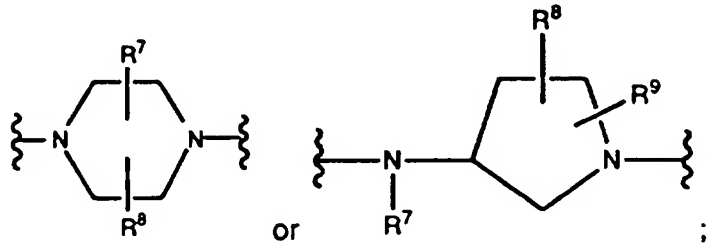
3. R^2 is



4. R^2 is



5. R1 is phenyl or phenyl mono-substituted with fluoro;
R^2 is



;

R^7 is hydrogen;
R^8 and R^9 are hydrogen or methyl;
n is 1;
R^3 is ethylene;
R^4 is phenyl disubstituted with methoxy and aminosulfonyl.

6. R^1 is phenyl mono or disubstituted with fluorine.

Suitable pharmaceutically acceptable salts of the compounds of formula (I) include acid addition salts formed with acids, e.g. hydrochlorides, hydrobromides, sulfates, alkyl- or arylsulfonates, phosphates, acetates, citrates, succinates, lactates, tartrates, fumarates, and maleates; and base salts such as alkali metal salts e.g. sodium salts. The solvates may, for example, be hydrates.

Other salts which are not pharmaceutically acceptable may be useful in the preparation of compounds of formula (I) and these form a further aspect of the invention.

It is to be understood that the present invention encompasses the individual enantiomers of the compounds represented by formula (I) above as well as wholly or partially racemic mixtures thereof. The present invention also covers the individual enantiomers of the compounds represented by formula (I) above as mixtures with diastereoisomers thereof in which one or more of the two stereocenters is inverted.

GENERAL CHEMISTRY PROCEDURES

Compounds of general formula (I) may be prepared by methods known in the art of organic synthesis, as shown in part by the following processes and schemes. For any of these processes and schemes, it may be necessary and/or desirable to protect sensitive or reactive groups . Protecting groups are employed according to standard methods of organic synthesis (T. W. Green and P. G. M. Watts (1991) Protecting Groups in Organic Synthesis, John Wiley & Sons). These groups are removed at a convenient stage of synthesis using methods known from the art. Thus, for example, amino groups may be protected by a group selected from aralkyl (e.g. benzyl), acyl, or sulfonyl, e.g. allylsulfonyl, phthalimide, or tosyl; subsequent removal of the protecting group being effected when desired by hydrolysis or hydrogenolysis as appropriate using standard conditions. Hydroxyl and carboxyl groups may be protected using any conventional hydroxyl or carboxyl protecting group. Examples of suitable hydroxyl and carboxyl protecting groups include groups selected from alkyl, e.g. methyl, tert-butyl, or methoxymethyl, aralkyl, e.g. benzyl, diphenylmethyl, or triphenylmethyl, heterocyclic groups such as

tetrahydropyranyl, acyl. e.g. acetyl or benzoyl, and silyl groups such as trialkylsilyl, e.g. tert-butyldimethylsilyl. The hydroxyl protecting groups may be removed by conventional techniques. Thus, for example, alkyl, silyl, acyl, and heterocyclic groups may be removed by hydrolysis under acidic or basic conditions. Aralkyl groups such as triphenylmethyl may similiarly be removed by hydrolysis under acidic conditions. Aralkyl groups such as benzyl may be cleaved by hydrogenolysis in the presence of a Noble metal catalyst such as palladium-on-charcoal. Silyl groups may also conveniently be removed using a source of fluoride ions such as tetra-n-butylammonium fluoride.

As used herein the symbols and conventions used in these processes, schemes and examples are consistent with those used in the contemporary scientific literature, for example, the Journal of the American Chemical Society. Unless otherwise noted, all starting materials were obtained from commercial suppliers and used without further purification. Specifically, the following abbreviations may be used in the examples and throughout the specification: g (grams); mg (milligrams); L (liters); mL (milliliters); psi (pounds per square inch); M (molar); mM (millimolar); i. v. (intravenous); Hz (Hertz); mol (moles); RT (room temperature); min (minutes); h (hours); m.p. (melting point); TLC (thin layer chromatography); MeOH (methanol); TFA (trifluoroacetic acid); THF (tetrahydrofuran); dimethylsulfoxide (DMSO); EtOAc (ethyl acetate); dichloromethane (DCM); dimethylformamide (DMF); 1, 1-carbonyldiimidazole (CDI); isobutylchloroformate (iBuCF); N-hydroxysuccinimide (HOSu); N-hydroxybenztriazole (HOBT); 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC); bis(2-oxo-3-oxazolidinyl) phosphinic chloride (BOP); tert-butyloxycarbonyl (BOC); dicyclohexylcarbodiimide (DCC); benzyloxycarbonyl (Cbz). All references to ether are to diethyl ether. Unless otherwise indicated, all temperatures are expressed in ^{o} C (degrees Centigrade). All reactions conducted at room temperature unless otherwise noted.

The ^{1}HNMR spectra were recorded on either a Varian VXR-300 or a Varian Unity-300 instrument. Chemical shifts are expressed in parts per million (ppm, δ units). Coupling constants are in units of hertz (Hz). Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad.

Low-resolution mass spectra (MS) were recorded on a JOEL JMS-AX505HA, JOEL SX-102 or a SCIEX-APIiii spectrometers. All mass spectra were taken in the

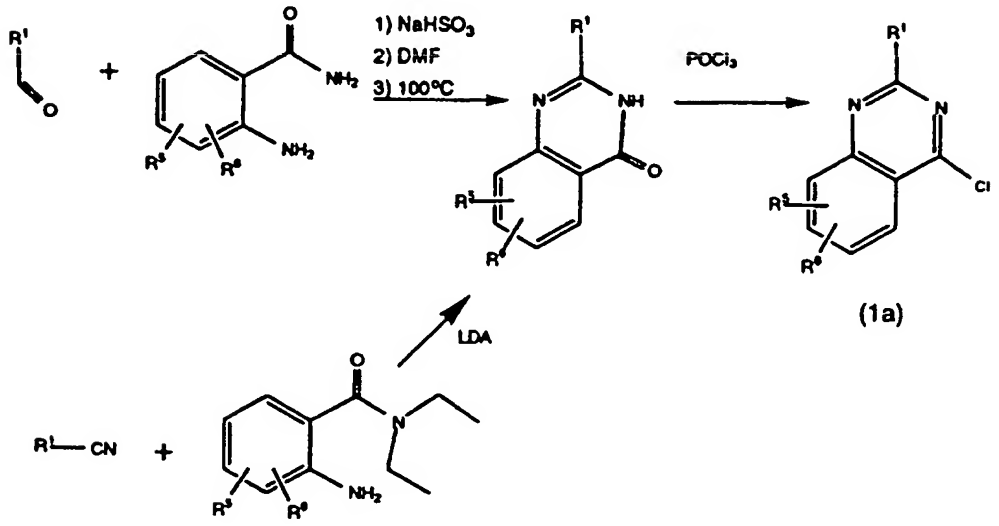
positive ion mode under electrospray ionization (ESI), chemical ionization (CI), electron impact (EI) or by fast atom bombardment (FAB) methods. Infrared (IR) spectra were obtained on a Nicolet 510 FT-IR spectrometer using a 1-mm NaCl cell. Rotations were recorded on a Perkin-Elmer 241 polarimeter. All reactions were monitored by thin-layer chromatography on 0.25 mm E. Merck silica gel plates (60F-254), visualized with UV light, 7% ethanolic phosphomolybdic acid, p-anisldehyde solution or iodine. Flash column chromatography was performed on silica gel (230-400 mesh, Merck).

Products were purified by preparative reversed phase high pressure liquid chromatography (RP-HPLC) using a Waters Model 3000 Delta Prep equipped with a Delta-pak radial compression cartridge (C_{18}, 300 A, 15μ, 47 mm X 300 mm). Linear gradients were used in all cases and the flow rate was approximately 100 mL/minute (t_0 = 5.0 min.). All solvents contained 0.1% TFA. Analytical purity was assessed by RP-HPLC using a Waters 600E system equipped with a Waters 990 diode array spectrometer (λ range 200-400 nM). The stationary phase was a Vydac C_{18} column (5μ, 4.6 mm X 250 mm). The flow rate was 1.0 to 1.5 ml/min. (t_0 = 2.8 or 3.0 min.) and the solvent systems were as described above. Data reported as tr, retention time in minutes (% acetonitrile over time).

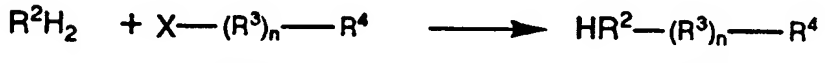
PG represents a suitable protecting group, examples of which, and means for the use and removal of which can be found in Protective Groups in Organic Synthesis, *supra*. LG represents a suitable leaving group, such as Cl, Br, mesylate or tosylate.

For the following Schemes 1-3 and Processes A-B; R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, m and n are defined as for formula (I) above.

Scheme 1



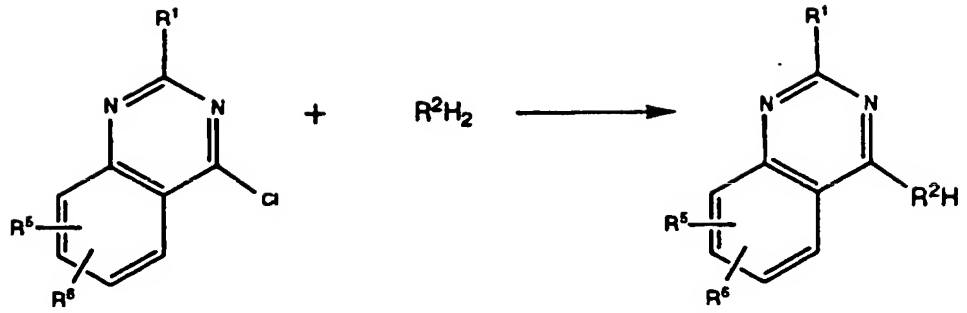
Scheme 2



(2a) (2b)

Wherein X is chlorine, bromine or iodine;

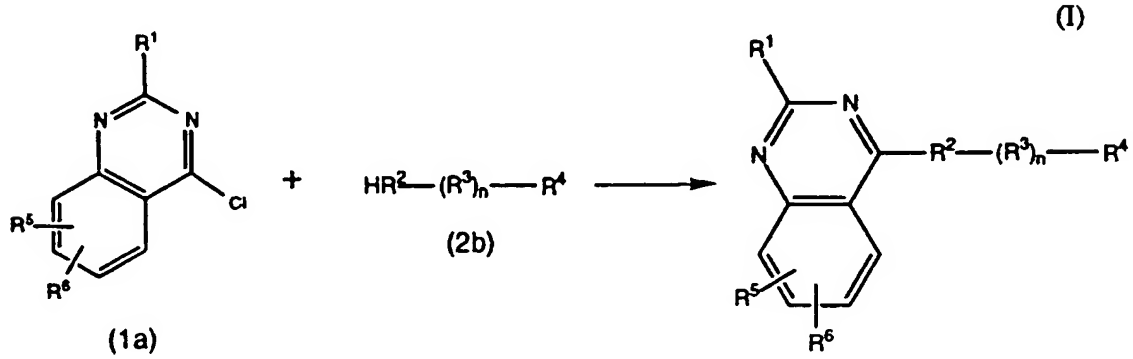
Scheme 3



(3a)

Process A

According to Process A, certain compounds of formula (I) may be prepared by the reaction of a compound of formula (1a), prepared as seen in Scheme 1, with a base of formula (2b), prepared as seen in Scheme 2:

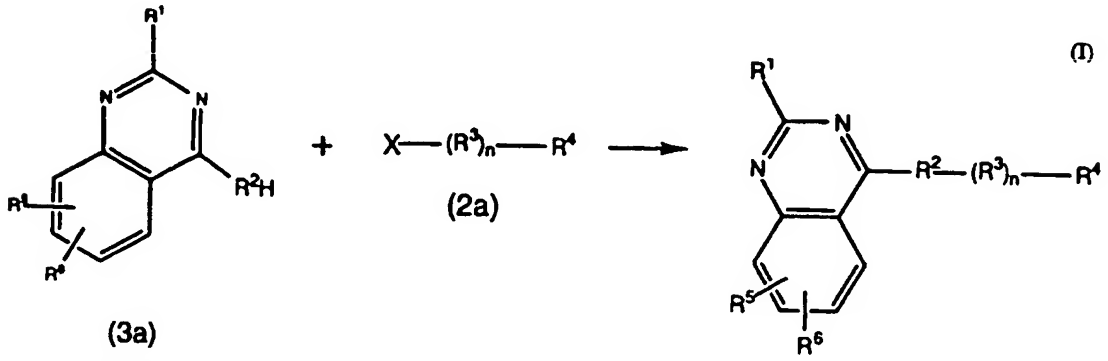


(1a) (2b) (I)

An excess of a second base such as potassium carbonate, triethylamine, sodium hydride or Hunig's base may be employed to drive the reaction to completion. The reactions may be run in a solvent like tetrahydrofuran, dioxane, ethanol or acetonitrile at elevated temperatures. Compounds of formula (I) may be converted to an appropriate salt form.

Process B

According to Process B, certain compounds of formula (I) may be prepared by the reaction of a compound of formula (3a), prepared as seen in Scheme 3, with halogen of formula (2a):



(3a) (2a) (I)

Wherein X is chlorine, bromine or iodine. An excess of a second base such as potassium carbonate, triethylamine or Hunig's base may be added to drive the reaction to completion. When X is chlorine or bromine, then sodium iodide may be added to generate the iodide *in situ*. The reactions may be run in a solvent such as tetrahydrofuran, dioxane, ethanol or acetonitrile at elevated temperatures. These products may be converted to an appropriate salt form.

Pharmacology

The efficacy of compounds of the present invention can be evaluated and measured using pharmacological methods known in the art or as described in detail below based on similarly established methodologies.

1. HUMAN α-1B, α-1C AND α-1D RECEPTOR BINDING ASSAYS

REFERENCES:

1. Cheng, Y.C. and Prusoff, W.H. Relationship between the inhibition constant (Ki) and the concentration of inhibitor which causes 50% inhibition of an enzymatic reaction. Biochem. Pharmacol. 22:3099-3108 (1973).

2. Lutz, M.W., Goetz, A.S., Morgan, P.H. and Rimele T.J. Statistical and graphical methods for analysis of radioligand binding experiments: Development of a RS/1 based tool palette. Proc. of BBN worldwide user meeting, p. 26 (1991).

METHOD:

Binding studies were performed in 96 well microtiter plates incubated at 25 degrees C for 90 min. Incubations (222 ul) contained 0.5 ug of protein, in a buffer consisting of 25 mM PIPES, 150 mM NaCl, 5 mM $MgCl_2$, 1 mM EDTA, pH 7.5 (assay buffer), approximately 75,000 cpm (70 pM) of [125I]I-HEAT, and displacing ligands or vehicle (3.0 % DMSO/25 mM HOAc in H_2O, 0.3 %/2.5 mM final concentration in assay) as appropriate. The reaction was terminated by rapid vacuum filtration through GF/B glass fiber filters, presoaked in 0.1% BSA for 30 min., using a Brandel cell harvester. The filters were washed with approximately 4 ml ice cold 25 mM Tris-HCL, pH = 7.4 buffer. Retained radioactivity was determined by gamma counting in a LKB gamma counter. Nonspecific binding was determined in the presence of 100 uM phentolamine and was usually <= 15% of total binding.

MATERIALS:

CELL CULTURE:

Rat-1 fibroblast cells expressing adrenergic receptor subtype were developed at Glaxo. Dulbecco's Modified Eagles Medium (D-MEM), trypsin-EDTA,

penicillin/streptomycin, geneticin were purchased from Gibco (Grand Island, N.Y.). Fetal bovine serum was purchased from Hyclone (Logan, Utah).

COMPOUNDS:

Phentolamine, albumin, bovine fraction V, were purchased from Sigma (St. Louis, MO); 5-CH_3-urapidil was purchased from Research Biochemicals Incorporated (Natick, MA)

RADIOLIGAND:

[125I]I-HEAT, specific activity 2200 Ci/mmol was purchased from New England Nuclear (Wilmington, DE).

PROCEDURE:

PREPARATION OF THE TEST COMPOUND

1. Dissolve compound in distilled water or dimethylsulfoxide according to solubility.

2. When a solvent is used, estimate the solvent effects on binding. Use a concentration that does not affect binding.

PREPARATION OF CELL MEMBRANE

1. Adherent rat-1 fibroblast cells expressing Alpha-1 adrenergic receptors were grown to 80-95% confluency in roller bottles, in D-MEM supplemented with 5% fetal bovine serum, penicillin/streptomycin (10 unit/10 ug/ml) and geneticin (500 ug/ml).

2. Cells were removed from flasks using trypsin/EDTA, washed in pbs, pelleted, washed and quick frozen on dry ice/EtOH. Cells were stored in -80 degrees C until needed.

*The following procedures were performed at 4 degrees C unless otherwise stated.

3. Frozen aliquots of cells were thawed at room temperature and suspended 50 mM Tris-HCL, 250 mM sucrose buffer, pH = 7.4, containing: 1 ug/ml aprotinin, 17 ug/ml PMSF, 20 ug/ml bacitracin, 1 mM benzamidine, 10 ug/ml leupeptin and 10 ug/ml pepstatin A.

4. The cells were disrupted using a Tekmar tissuemizer, setting 5 for 30 seconds, then homogenized in a dounce homogenizer by 10 strokes with a tight fitting pestle.

5. The homogenate was centrifuged at 100,000 x g for 30 min. (Sorvall F28/36 rotor, 28,000 RPM).

6. The resulting pellet was resuspended in centrifugation buffer (10 mM Tris-HCl, pH 7.4), homogenized and centrifuged as previously described.

7. The pellets were collected, suspended in centrifugation buffer and protein concentration was determined by BIO-RAD. Bovine serum albumin was used as the standard.

8. Aliquots were stored at -80 degrees C until assayed. Binding was stable for at least 6 months under these storage conditions.

PERFORMING THE EXPERIMENT

1. Binding studies were performed in 96 well microtiter plate at 25 degrees C incubated for 90 min.

2. Incubations (222 ul) contained 0.5 ug of protein, in a buffer consisting of 25 mM PIPES, 150 mM NaCl, 10 mM $MgCl_2$, 1 mM EDTA, pH 7.5 (assay buffer).

3. Approximately 75,000 cpm (70 pM) of [125I]I-HEAT, and displacing ligands or vehicle (3.0 % DMSO/25 mM HOAc in H_2O, 0.3 %/2.5 mM final concentration in assay) as appropriate.

4. The reaction was terminated by rapid vacuum filtration through GF/B glass fiber filters, presoaked in 0.1% BSA for 30 min., using a Brandel cell harvester.

5. The filters were washed with approximately 4 ml ice cold 25 mM Tris-HCL, pH = 7.4 buffer and punched into tubes.

DATA COLLECTION AND ANALYSIS:

COLLECTING THE DATA

Retained radioactivity (in filter) was determined by gamma scintillation counting as total binding. Specific binding is determined by subtracting the non-specific binding from the total binding and subsequently processed by RADLIG.

CALCULATING THE PKI

The IC50 represents the concentration of inhibitor giving 50% decrease of binding relative to control. Ki values were calculated by the method of Cheng and Prusoff. (1) The pKi is the -log of the Ki (inhibition constant). The Ki is also termed a compound's affinity for the receptor.

1. Competition curves were fit to models of ligand binding to single and multiple receptor sites implemented in the RS/1 (BNN Software Products, Cambridge MA, version 4.2) statistical analysis program called RADLIG.(2)

2. A partial F-test was used to discriminate between one and two site models.

3. The Ki is calculated from the fit of the curve to a single receptor site if the Hill coefficient (N) is not statistically different from unity (constrained

model). If the Hill coefficient is greater than unity, the Ki is calculated from the fit of the curve to the unconstrained model. If the Hill coefficient is less than unity and a multiple receptor site model is a significantly better fit, the Ki is calculated from the fit of the curve to a multiple receptor site and multiple Kis are calculated.

Table 1: Relative Functional Receptor Binding Activity

Example Number	Human α-1B	Human α-1C	Human α-1D
1	+	++	+
2	++	++	++
3	+++	+++	++
4	++	+++	++
5	+	+	+
6	++	++	++
7	++	+	++
8	+	+	+
9	++	++	++
10	+	++	++
11	+	+	+
12	+	+	+
13	++	++	++
14	+	+	+
15	++	+++	++
16	++	+++	++
17	+++	+++	++
18	++	++	++
19	++	++	+
20	++	+	+
21	++	+++	++
22	++	++	+

	23	++	++	++
	24	+	+	+
	25	+++	+++	++
	26	+	+	+
5	27	+	+	+
	28	++	++	+
	29	++	++	++
	30	++	++	++
	31	++	+++	++
10	32	+++	+++	+++
	33	+++	+++	++
	34	+++	+++	++
	35	++	++	++
	36	+	+	+
15	37	++	+	++
	38	++	++	+
	39	++	++	++
	40	++	++	+
	41	++	++	++
20	42	++	+++	++
	43	+++	+++	++
	44	+++	+++	++
	45	+++	++	++
	46	+++	+++	++
25	47	+++	+++	++
	55	+++	+++	+++
	56	+++	+++	++
	57	++	+++	++
	58	+	++	+
30	59	+++	+++	+++
	60	+	++	+
	61	+	++	+
	62	+++	+++	++

	63	+++	+++	+++
	64	+++	+++	++
	65	++	++	+
	66	++	++	++
5	67	++	++	+
	68	+++	+++	++
	69	+++	+++	++
	70	++	+++	++
	71	+++	+++	++
10	72	++	++	+
	73	++	++	+
	74	++	++	+
	75	++	++	+
	76	++	++	+
15	77	++	++	+
	78	+	+	+
	79	+	+	+
	80	+++	++	++
	81	+++	+++	++
20	82	+	+	+
	83	+	++	+
	84	+	+	+
	85	++	++	+
	86	+++	+++	++
25	87	+++	+++	++
	88	+++	+++	++
	89	+++	+++	++
	90	++	++	++
	91	++	+++	++
30	92	+	++	+
	93	+	+	+
	94	++	++	++
	95	+++	+++	++

96	+	+	+
97	+	++	+

2. TISSUE ASSAYS

A. CANINE URETHRAL-PROSTATE PRESSURE

PURPOSE:

To evaluate the ability of compounds to affect urethral-prostate pressure (contractility) while assessing their cardiovascular effects simultaneously.

METHOD:

Using hypogastric nerve stimulation (NS) and the α-1 agonist phenylephrine (or other receptor agonists, as appropriate) the responses of urethral pressures and systemic blood pressure are recorded. The tests compounds are then given in a log dose infusion. The inhibition of the NS response within the prostate as well as the systemic phenylephrine response on blood pressure is measured to assess the uro-selectivity of the compound in the anesthetized dog.

INTERPRETATION:

Interesting compounds are those that express uro-selectivity with a ratio of >100 for the urethral pressure vs diastolic blood pressure comparisons (BP/US).

DETAILED DESCRIPTION:

MATERIALS:

SPECIES:

Male mongrel dogs (10-20 kg)

ANESTHESIA:

1. Nembutal (pentobarbital sodium) 50 mg/ml, Abbott Laboratories.

2. Barbital (sodium salt) No. B-0500, Sigma Chemicals.

LABORATORY CHEMICALS AND SOLUTIONS

Phenylephrine Hydrochloride Injection (1%), Schein.

Compound Vehicle Solution
0.05N HCL in distilled water.

Bladder Perfusion Solution
Sodium Chloride 0.9% (L8000), Kendall McGraw Labs.

IV Flush Solution
Isotonic Saline (Cat B3158-1), Baxter Health Care.

Heparin Sodium
1000 u/ml, Elkins Sinn Inc.

GENERAL LABORATORY EQUIPMENT:

Urethral Catheter Size 8 Fr x 16" HRI 8890 700811, Sovereign.

Harvard Ventilator Model 613, Harvard Apparatus.

IL 1306 Blood Gas Analyzer, Instrumentation Laboratories.

Surgistat Model B Electro cautery, ValleyLabs.

Model K20 Heating pad, Baxter Health Care.

Grass Stimulator Model S88E

Harvard Dastre Electrode # 50-6873

RECORDING EQUIPMENT:

Gould 3800S Physiograph

Micron Model MP15D Transducer

Modular Instruments Inc. On-line data acquisition system

PROCEDURE:

PREPARATION OF THE TEST COMPOUND:

1. Dissolve compound in a 0.05N HCL (50 ml of 1N of HCL in 1L of distilled water).

2. Depending on drug solubility addition of heat may be necessary (temp as high as 60° C).

3. All doses are to be given on a ug/kg (salt) dose.

PREPARATION OF ALPHA AGONIST:

1. Phenylephrine 1% solution (10mg/ml), 1 ml to 250 ml of isotonic saline (40 ug/ml), bolus dose 10 ug/kg (salt).

PREPARATION OF THE ANESTHETIZED DOG:

1. Animals are given a combination of Na-pentobarbital (15 mg/kg) and Na-barbital (300 mg/kg) IV. intubated with a cuffed endotracheal tube and placed on a ventilator (Harvard Apparatus, model 613, South Natick, MA with room air.)

2. Ventilation parameters are adjusted to maintain normal arterial blood gases. Standard settings are 12-24 respirations per minute and tidal volumes of 12-15 ml per kg.

3. A continuous infusion of pentobarbital is maintained throughout the duration of the experiment (3 mg/kg/hr).

4. Rectal temperature is monitored and maintained at 37-39° C with a heating pad.

5. The femoral artery and vein are cannulated for blood pressure monitoring and infusion of drugs are anesthesia. The cephalic vein which is used for initial anesthesia induction is now used for the phenylephrine IV bolus injection.

ATTACHING THE ELECTRODE AND INSERTING THE CATHETER

1. A midline laparotomy is used to open the abdomen, and the hypogastric nerves are isolated from surrounding tissue and sectioned approximately 1 cm distal to the inferior mesenteric ganglion.

2. A bipolar electrode is then attached to the distal end of the ligated nerve. Using the same incision the bladder, prostate and the urethra are identified. The bladder is incised in the dome and two catheters are inserted through the bladder. One catheter is used for urine drainage and the other inserted antegrade into the prostatic urethra.

One suture is tied around the urethra distal to the prostate and another ligature secured proximally, around the bladder neck without occluding the ureters. A third suture is placed around both catheters at the bladder dome to stabilize preparation and allow urine to be collected externally.

3. The baseline pressure within the prostate is then adjusted to a level of 15 to 20 mmHg by addition of normal saline into the catheter. All incisions are then closed. The effects of either nerve stimulation (NS) or IV phenylephrine can be evaluated.

PERFORMING THE EXPERIMENT:

1. After a control period of at least 30 minutes and establishment of stable baselines of urethral and blood pressure are observed, the control responses to NS or phenylephrine bolus are recorded.

2. A hypogastric nerve stimulation of 16 Hertz, 10 Volts, 10 msec pulse width and 10 sec train duration are given and changes in urethral pressures are recorded.

3. At a time point 5 minutes post NS a phenylephrine bolus (10 ug/kg) is given into the cephalic vein and changes in blood pressure are recorded. At least two NS and phenylephrine injections are performed and evaluated for their consistency, the second consistent stimulation is picked for the baseline value response.

4. The test compound is then administered in a cumulative log dose infusion in the femoral vein (0.1 ml/kg/min) over 5 min. Doses of antagonist and dual stimulations are alternated at 10 and 15-min intervals until the highest dose of the antagonist is administered, usually 0.3-1.0 mg/kg. The effect of the antagonist on both the baseline systemic and urethral pressures as well as the % inhibition of the NS and phenylephrine responses is recorded.

DATA COLLECTION AND ANALYSIS:

The data is collected in three forms, raw data sheets, polygraph recording paper and on-line data acquisition system files. The pressure determinations are made from the graphics mode created from the Modular Instruments computer system. This method allows more precise measurements to be made because of the faster sampling times of the pressure curves. The data is then transferred to RS1 tables and graphs. The determination of the urethral and blood pressure values are calculated from a RS1 program for best curve fitting. From these curves the following measures are calculated:

UP ED50 (ug/kg): The dose of the test compound (salt) which produces 50% inhibition of the NS (nerve stimulation) response on urethral pressure.

BP ED50 (ug/kg): The dose of the test compound (salt) which produces 50% inhibition of the agonist response on diastolic blood pressure.

BP/UP: The ratio of the BP ED50 to the UP ED50.

DBP-ED25 (ug/kg): The dose of the test compound (salt) which produces 25% inhibition of the agonist response on diastolic blood pressure.

UP-ED80 (ug/kg): The dose of the test compound (salt) which produces 80% inhibition of the NS (serve stimulation) response on urethral pressure.

%I-DBP: The percent inhibition of the diastolic blood pressure at the dose producing 80% inhibition of urethral pressure.

%Dec BP: The percent decrease of diastolic blood pressure at the dose producing 80% inhibition of the urethral pressure.

ED20BP (ug/kg): The dose of the test compound (salt) that decreases the diastolic blood pressure 20 mmHg from the baseline value.

While it is possible that, for use in therapy, a compound of the invention may be administered as the raw chemical it is possible to present the active ingredient as a pharmaceutical formulation. The invention thus further provides a pharmaceutical formulation comprising a compound of formula (I) or a physiologically acceptable salt or solvate thereof together with one or more pharmaceutically acceptable carriers or excipients. The carrier(s) or excipient(s) must be acceptable in the sense of being compatable with the other ingredients of the formulation and not deleterious to the recipient thereof. According to another aspect of the invention, there is provided a process for the preparation of a pharmaceutical formulation comprising admixing a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof with one of more pharmaceutically acceptable carriers or excipients.

Compounds of formula (I) and physiologically acceptable salts and solvates thereof may be formulated for administration by any route, and the appropriate route will depend on the disease being treated. Suitable pharmaceutical formulations include those for oral, rectal, nasal, topical (including buccal and sublingual), vaginal or parental (including intramuscular, sub-cutaneous, intravenous, and directly into the affected tissue) administration or in a form suitable for administration by inhalation or insufflation. The formulations may, where appropriate, be conveniently presented in discrete dosage units and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing into association the active compound with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

Pharmaceutical formulations suitable for oral administration may conveniently be presented as discrete units such as capsules, cachets, or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution, a suspension or as an emulsion. The active ingredient may also be presented as a bolus, electuary, or paste. Tablets and capsules for

oral administration may contain conventional excipients such as binding agents, fillers, lubricants, disintegrants, or wetting agents. The tablets may be coated according to methods well known in the art. Timed release formulations which are known in the art may also be suitable. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs, or may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, non-aqueous vehicles (which may include edible oils), or preservatives.

The compounds according to the invention may also be formulated for parental administration (e.g. by injection, for example bolus injection or continuous infusion) and may be presented in unit dose form in ampules, pre-filled syringes, small volume infusion or in muti-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing, and/or dispersing agents. Alternatively, the active ingredient may be in powder form, obtained by asceptic isolation of sterile solid or by lyophilization from solution, for constitution with a suitable vehicle, e.g. sterile, pyrogen free water, before use.

For topical administration to the epidermis the compounds according to the invention may be formulated as ointments, creams or lotions, or as a transdermal patch. Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilizing agents, suspending agents, thickening agents, or coloring agents. Formulations suitable for topical administration in the mouth include lozenges comprising active ingredient in a flavored base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert base such as gelatin and glycerin or sucrose and acacia; and mouth washes comprising the active ingredient in a suitable liquid carrier. For topical administration to the eye, the compounds according to the invention may be made up in a solution or suspension in a suitable sterile aqueous or non-aqueous vehicle. Additives such as buffers (e.g.

sodium metabisulphite or disodium edeate) and thickening agents such as hypromellose may also be included.

Pharmaceutical formulations suitable for rectal administration wherein the carrier is a solid are possibly presented as unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art, and the suppositories may be conveniently formed by admixture of the active compound with the softened or melted carrier(s) followed by chilling and shaping in moulds.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams, or sprays containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

For intra-nasal administration the compounds of the invention may be used as a liquid spray or dispersible powder or in the form of drops. Drops may be formulated with an aqueous or non-aqueous base also comprising one or more dispersing agents, solubilizing agents, or suspending agents. Liquid sprays are conveniently delivered from pressurized packs.

For administration by inhalation the compounds according to the invention are conveniently delivered from an insufflator, nebulizer or a pressurized pack or other convenient means of delivering the aerosol spray. Pressurized packs may comprise a suitable propellant such as dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount.

Alternatively, for administration by inhalation or insufflation, the compounds according to the invention may take the form of a dry powder composition, for example a powder mix of the compound and a suitable powder base such as lactose or starch. The powder composition may be presented in unit dosage form in, for example, capsules or cartridges or e.g. gelatin of blister packs from which the powder may be administered with the aid of an inhalator or insufflator.

When desired the above described formulations adapted to give sustained release of the active ingredient may be employed.

The compounds and pharmaceutical compositions of the invention may also be used in combination with other therapeutic agents, for example antiinfective agents such as bactericidal or fungicidal agents, antiinflammatory agents or anticancer agents. In particular testosterone 5α–reductase inhibitors or dopamine D_2 antagonists in combination with compounds and pharmaceutical compositions of the present invention may be used.

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically acceptable carrier thereof comprise a further aspect of the invention. The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations. Appropriate doses of known therapeutic agents will be readily appreciated by those skilled in the art.

The amount of a compound of the invention required for use in treatment will of course vary not only with the particular compound selected but also with the route of administration, the nature of the condition being treated and the age and condition of the patient and will be ultimately at the discretion of the attendant physician. In general, however, a suitable dose will be in the range of from about 0.1 to 300 mg/kg of bodyweight per day, particularly from about 1 to 100 mg/kg of bodyweight per day. An appropriate dosage unit involved in oral administration may generally contain from about 1 to 250 mg, particularly from about 25 to 250 mg, of a compound of formula (I). The dosage employed for the topical administration will, of course, depend on the size of the area being treated. For the eyes each dose will be typically in the range of from 10 to 100 mg of the compound of formula (I).

For use in the treatment of α-1C related disorders, in particular benign prostatic hyperplasia, the compounds of the invention can be administered by any of the aforementioned routes, particularly by the oral route or by injection. The daily dosage for a 70 kg mammal will be in the range of about 5 mg to 5 g of a compound of formula (I).

EXAMPLES

The following examples illustrate aspects of this invention but should not be construed as limitations thereto.

Intermediate 1

4-[1,4]Diazepan-1-yl-2-phenyl-quinazoline

A solution of 4-chloro-2-phenyl-quinazoline (5.00 g, 20.77 mmol) in tetrahydrofuran (100 ml) is added to a solution of homopiperazine (10.40 g, 103.87 mmol) in tetrahydrofuran (108 ml) and the solution is heated at reflux for 17 h. The solution is concentrated, saturated sodium carbonate is added, and the mixture is extracted with ethyl acetate. The combined organic layers are dried with magnesium sulfate and concentrated. The residue is purified by silica gel chromatography using methanol:ethyl acetate (1:7) containing 1% ammonium hydroxide as eluant to give the title compound (6.21 g):
^{1}H NMR ($CDCl_3$) δ 8.54-8.49 (m, 2H), 7.94-7.89 (m, 2H), 7.64 (dt, 1H, J = 7, 1 Hz), 7.49-7.40 (m, 3H), 7.32-7.27 (m, 1H), 4.06-4.02 (m, 4H), 3.19 (dt, 2H, J = 5, 3 Hz), 2.93 (t, 2H, J = 6 Hz), 2.10-2.03 (m, 2H), 1.79 (s, 1H);
FAB MS *m/z* found 305 (MH^+).

Intermediate 2

1-(2-Phenyl-quinazolin-4-yl)-piperidin-4-yl-amine

A. (1-Benzyl-piperidin-4-yl)-(2-phenyl-quinazolin-4-yl)-amine

Synthesized in a manner similar to Intermediate 1, using 4-Chloro-2-phenyl-quinazoline (5.00 g, 20.77 mmol) and 4-amino-1-benzyl-piperidine (7.91 g, 41.55 mmol) to give (1-Benzyl-piperidin-4-yl)-(2-phenyl-quinazolin-4-yl)-amine (8.08 g):

^{1}H NMR ($CDCl_3$) δ 8.52 (dd, 2H, *J* = 8, 2 Hz), 7.90 (d, 1H, *J* = 8 Hz), 7.73-7.64 (m, 2H), 7.51-7.26 (m, 9H), 5.54 (d, 1H, *J* = 7 Hz), 4.46-4.41 (m, 1H), 3.57 (s, 2H), 2.93 (d, 2H, *J* = 12 Hz), 2.33-2.21 (m, 4H), 1.73-1.65 (m, 2H);
FAB MS *m/z* found 395 (MH^+).

B. (2-Phenyl-quinazolin-4-yl)-piperidin-4-yl-amine

Ammonium formate (6.46 g, 102.40 mmol) is added to a solution of (1-benzyl-piperidin-4-yl)-(2-phenyl-quinazolin-4-yl)-amine (8.08 g, 20.48 mmol), prepared as in Part A, in methanol (102 ml) under argon. Then, 10% palladium on carbon (2.02 g, 25wt%) is added and the solution is heated at reflux for 20 h. The solution is purged with nitrogen, filtered through Celite®, and concentrated. The residue is purified by silica gel chromatography using methanol:ethyl acetate (3:2) containing 1% ammonium hydroxide as eluant to give the title compound (5.73 g):
^{1}H NMR (CD_3OD) δ 8.40-8.35 (m, 2H), 8.11 (dd, 1H, *J* = 8, 1 Hz), 7.78 (d, 1H, *J* = 8 Hz), 7.70 (dt, 1H, *J* = 7, 1 Hz), 7.48-7.38 (m, 4H), 4.52-4.44 (m, 1H), 3.11 (d, 2H, *J* = 13 Hz), 2.75 (dt, 2H, *J* = 13, 2 Hz), 2.12 (dd, 2H, *J* = 12, 2), 1.61 (dq, 2H, *J* =12, 4 Hz);
FAB MS *m/z* found 305 (MH^+).

Intermediate 3

4-(3-Methyl-piperazin-1-yl)-2-phenyl-quinazoline

Synthesized in a manner similar to Intermediate 1, using 4-Chloro-2-phenyl-quinazoline (5.00 g, 20.77 mmol) and 2-methyl-piperazine (10.40 g, 103.87 mmol) to give the title compound (6.15 g):
^{1}H NMR ($CDCl_3$) δ 8.55-8.52 (m, 2H), 7.93 (d, 1H, *J* = 8 Hz), 7.81 (d, 1H, *J* = 8 Hz), 7.66 (dt, 1H, *J* = 7, 1Hz), 7.50-7.40 (m, 3H), 7.34 (dt, 1H, *J* = 7, 1 Hz), 4.31-4.23 (m, 2H), 3.25-3.12 (m, 1H), 3.08-3.00 (m, 3H), 2.84 (dd, 1H, *J* = 13, 10 Hz), 1.84 (s, 1H), 1.10 (d, 3H, *J* = 6.4 Hz);
FAB MS *m/z* found 305 (MH^+).

Intermediate 4

5-[2-(3-Amino-piperidin-1-yl)-ethyl]-2-methoxy-benzenesulfonamide

Sodium iodide (1.08 g, 7.22 mmol) is added to 3-amino-piperidine dihydrochloride (1.25 g, 7.22 mmol) in 1,4-dioxane (36 ml). Then, N,N-di-*iso*-propylethyl amine (5.05 ml, 28.89 mmol) is added to the mixture. Finally, 5-(2-chloro-ethyl)-2-methoxy-benzenesulfonamide (1.80 g, 7.22 mmol) is added to the mixture and it is heated at reflux for 14 h. The reaction is cooled and concentrated. The residue is purified by silica gel chromatography using methanol:ethyl acetate (3:2) containing 1% ammonium hydroxide as eluant to give the title compound (790.9 mg):
^{1}H NMR (CD_3OD) δ 7.72 (d, 1H, J = 2 Hz), 7.47 (dd, 1H, J = 9, 2 Hz), 7.14 (d, 1H, J = 9 Hz), 3.44-3.40 (m, 1H), 3.34 (s, 3H), 3.13-3.07 (m, 1H), 2.93-2.82 (m, 4H), 2.65-2.60 (m, 2H), 2.03-1.85 (m, 2H), 1.77-1.56 (m, 2H), 1.39-1.37 (m, 1H);
FAB MS *m/z* found 314 (MH^+).

Intermediate 5

5-[2-(3-Amino-azepan-1-yl)-ethyl]-2-methoxy-benzenesulfonamide

Sodium iodide (1.31 g, 8.76 mmol) is added to 3-amino-azepine (1.00 g, 8.76 mmol, Oguchi, *et al, J. Appl. Polym. Sci.* 1984, *29*, 4341.) in 1,4-dioxane (44 ml). Then, potassium carbonate (1.21 g, 8.76 mmol) is added to the mixture. Finally, 5-(2-chloro-ethyl)-2-methoxy-benzenesulfonamide (2.19 g, 8.76 mmol) is added to the mixture and it is heated at reflux for 15 h. The reaction is cooled and concentrated. The residue is purified by silica gel chromatography using methanol containing 1% ammonium hydroxide as eluant to give the title compound (617.2 mg):
^{1}H NMR (CD_3OD) δ 7.71 (d, 1H, J = 2 Hz), 7.42 (dd, 1H, J = 8, 2 Hz), 7.11 (d, 1H, J = 9 Hz), 3.95 (s, 3H), 2.97-2.90 (m, 1H), 2.87-2.64 (m, 7H), 2.52 (dd, 1H, J = 13, 7 Hz), 1.83-1.61 (m, 4H), 1.57-1.43 (m, 2H);
FAB MS *m/z* found 328 (MH^+).

Intermediate 6

5-[2-(3,5-Dimethyl-piperazin-1-yl)-ethyl]-2-methoxy-benzenesulfonamide

Synthesized in a manner similar to Intermediate 5, using 2,6-dimethyl-piperazine (11.43 g, 100.11 mmol) in 1,4-dioxane (200 ml) and 5-(2-chloro-ethyl)-2-methoxy-benzenesulfonamide (5.00 g, 20.02 mmol) to give the title compound (2.58 g):
^{1}H NMR (CD_3OD) δ 7.70 (d, 1H, J = 2 Hz), 7.43 (dd, 1H, J = 9, 2 Hz), 7.11 (d, 1H, J = 9 Hz), 3.95 (s, 3H), 3.05-2.94 (m, 4H), 2.80 (dd, 2H, J = 10, 7 Hz), 2.58 (dd, 2H, J = 10, 7 Hz), 1.80 (t, 2H, J = 11 Hz), 1.13 (d, 6H, J = 6 Hz);
FAB MS *m/z* found 328 (MH^+).

Intermediate 7

5-[2-(3-Methyl-piperazin-1-yl)-ethyl]-2-methoxy-benzenesulfonamide

Sodium iodide (300.1 mg, 2.00 mmol) is added to 2-methyl-piperazine (10.03 g, 100.11 mmol) in 1,4-dioxane (200 ml). Then, potassium carbonate (2.77 g, 20.02 mmol) is added to the mixture. Finally, 5-(2-chloro-ethyl)-2-methoxy-benzenesulfonamide (5.00 g, 20.02 mmol) is added to the mixture and it is heated at reflux for 19 h. The solution is cooled, water is added, and the mixture is extracted with ethyl acetate. The combined organic layers are dried with magnesium sulfate and concentrated. The residue is purified by silica gel chromatography using methanol:ethyl acetate (3:2) containing 1% ammonium hydroxide as eluant to give the title compound (689.2 mg):
^{1}H NMR (CD_3OD & $CDCl_3$) δ 7.69 (s, 1H), 7.39 (d, 1H, J = 9 Hz), 7.06 (d, 1H, J = 8 Hz), 3.95 (s, 3H), 2.97-2.76 (m, 7H), 2.54 (dd, 2H, J = 9, 7 Hz), 2.07 (dt, 2H, J = 11, 4 Hz), 1.76 (t, 1H, J = 11 Hz), 1.05 (d, 3H, J = 6 Hz);
FAB MS *m/z* found 314 (MH^+).

Intermediate 8

1-(2-Phenyl-quinazolin-4-yl)-piperadin-4-yl-amine

A. 1,1-Dimethyl-ethyl-oxycarbonyl-[1-(2-phenyl-quinazolin-4-yl)-piperidin-4-yl]-amine

4-Chloro-2-phenyl-quinazoline (1.20 g, 4.99 mmol) is added to a solution of 4-[(1,1-dimethylethyl)-oxycarbonylamino]-piperidine (1.00 g, 4.99 mmol, Heitsch, H. *et al*, *J. Med. Chem.* 1993, *36*, 2788.) in tetrahydrofuran (25 ml). Then, triethylamine (0.70 ml, 4.99 mmol) is added and the solution is heated at 50°C for 17 h. The solution is concentrated, saturated sodium carbonate is added, and the mixture is extracted with ethyl acetate. The combined organic layers are dried with magnesium sulfate and concentrated. The residue is purified by silica gel chromatography using ethyl acetate:hexanes (1:3) as eluant to give 1,1-dimethyl-ethyl-oxycarbonyl-[1-(2-phenyl-quinazolin-4-yl)-piperidin-4-yl]-amine (1.94 g): ^{1}H NMR ($CDCl_3$) δ 8.54-8.51 (m, 2H), 7.94 (d, 1H, J = 8 Hz), 7.83 (d, 1H, J = 8 Hz), 7.69 (dt, 1H, J = 8, 1 Hz), 7.50-7.44 (m, 3H), 7.38 (t, 1H, J = 7 Hz), 4.55 (br d, 1H, J = 6 Hz), 4.34 (d, 2H, J = 13 Hz), 3.80-3.79 (m, 1H), 3.30 (t, 2H, J = 12 Hz), 2.12 (dd, 2H, J = 13, 3 Hz), 1.64 (dq, 2H, J = 11, 3 Hz), 1.44 (s, 9H);
FAB MS *m/z* found 405 (MH^+).

B. 1-(2-Phenyl-quinazolin-4-yl)-piperadin-4-yl-amine

Trifluoroacetic acid:water:anisole (8:1:1, 24 ml) is added to the 1,1-dimethyl-ethyl-oxycarbonyl-[1-(2-phenyl-quinazolin-4-yl)-piperidin-4-yl]-amine (1.94 g, 4.80 mmol), prepared as in Part A, and the reaction is stirred for 16 h. The solution is concentrated, saturated sodium carbonate is added, and the mixture is extracted with ethyl acetate. The combined organic layers are dried with magnesium sulfate and concentrated. The residue is purified by silica gel chromatography using methanol:ethyl acetate (1:4) containing 1% ammonium hydroxide as eluant to give the title compound (1.44 g):

^{1}H NMR ($CDCl_3$) δ 8.51 (dd, 2H, J = 8, 2 Hz), 7.92 (d, 1H, J = 8 Hz), 7.79 (d, 1H, J = 8 Hz), 7.66 (dt, 1H, J = 8, 1 Hz), 7.49-7.39 (m, 3H), 7.34 (t, 1H, J = 7 Hz), 4.34 (d, 2H, J = 13 Hz), 3.23 (s, 2H), 3.16 (t, 2H, J = 14 Hz), 3.03 (p, 1H, J = 4 Hz), 1.98 (d, 2H, J = 11 Hz), 1.61 (dq, 2H, J = 11, 2 Hz);
FAB MS *m/z* found 305 (MH^+).

Intermediate 9

N 2-Benzyl-N 2-methyl-pyridine-2,5-diamine

A. Benzyl-(5-nitro-pyridin-2-yl)-methyl-amine

N-benzyl-methyl amine (1.53 g, 12.61 mmol) is added to a solution of 5-nitro-2-chloro-pyridine (1.00 g, 6.31 mmol) in tetrahydrofuran (3.1 ml) and the solution is heated at 150°C in a sealed tube for 19 h. The solution is concentrated, saturated sodium carbonate is added, and the mixture is extracted with ethyl acetate. The combined organic layers are dried with magnesium sulfate and concentrated. The residue is purified by silica gel chromatography using ethyl acetate:hexanes (1:4) as eluant to give benzyl-(5-nitro-pyridin-2-yl)-methyl-amine (1.53 g):
^{1}H NMR ($CDCl_3$) δ 9.06 (d, 1H, J = 2 Hz), 8.17 (dd, 1H, J = 9, 3 Hz), 7.35-7.25 (m, 3H), 7.19 (d, 2H, J = 7 Hz), 6.47 (d, 1H, J = 9 Hz), 4.90 (s, 2H), 3.16 (s, 3H);
FAB MS *m/z* found 244 (MH^+).

B. N 2-Benzyl-N 2-methyl-pyridine-2,5-diamine

Iron (1.66 g, 29.80 mmol) is added to a solution of benzyl-(5-nitro-pyridin-2-yl)-methyl-amine (1.45 g, 5.96 mmol), prepared as in Part A, in ethanol (24 ml). Then, concentrated hydrochloric acid (0.99 ml, 11.92 mmol) is added and the solution is heated at reflux for 3 h. The solution is cooled, filtered, concentrated, saturated sodium carbonate is added, and the mixture is extracted with ethyl acetate. The combined organic layers are dried with magnesium sulfate and concentrated. The residue is purified by silica gel chromatography using ethyl acetate:hexanes (3:2) as eluant to give the title compound (1.20 g):

^{1}H NMR ($CDCl_3$) δ 7.77 (d, 1H, *J* = 3 Hz), 7.30-7.19 (m, 5H), 6.93 (dd, 1H, *J* = 9, 3 Hz), 6.40 (d, 1H, *J* = 9 Hz), 4.67 (s, 2H), 3.16 (br s, 2H), 2.98 (s, 3H);
FAB MS *m/z* found 214 (MH^+).

Intermediate 10

Methyl-[3-(2-phenyl-quinazolin-4-yl)-propyl]-amine

A. 2-(2-Phenyl-quinazolin-4-yl)-malonic acid dibenzyl ester

Sodium hydride (1.04 g of 60% dispersion, 25.97 mmol) is added to a solution of dibenzyl malonate (7.09 g, 24.93 mmol) in tetrahydrofuran (104 ml) at 0°C under argon. Then, 4-chloro-2-phenyl-quinazoline (5.00 g, 20.77 mmol) is added and the solution is heated at reflux for 16 h. The solution is cooled, water is added, and the mixture is extracted with ethyl acetate. The combined organic layers are dried with magnesium sulfate and concentrated. The residue is purified by silica gel chromatography using ethyl acetate:hexanes (1:12) as eluant to give 2-(2-phenyl-quinazolin-4-yl)-malonic acid dibenzyl ester (3.45 g):
^{1}H NMR ($CDCl_3$) δ 8.56-8.54 (m, 2H), 8.19-8.17 (m, 1H), 8.10 (d, 1H, *J* = 9 Hz), 7.86 (t, 1H, *J* = 7 Hz), 7.77 (t, 2H, *J* = 8 Hz), 7.66-7.56 (m, 3H), 7.50-7.45 (m, 4H), 7.37-7.34 (m, 4H), 7.12 (t, 1H, *J* = 7 Hz), 5.71 (s, 1H), 5.30 (s, 4H);
FAB MS *m/z* found 489 (MH^+).

B. 2-[2-(Benzyl-methyl-amino)-ethyl]-2-(2-phenyl-quinazolin-4-yl)-malonic acid dibenzyl ester

Sodium hydride (163.7 mg of 60% dispersion, 4.09 mmol) is added to a solution of 2-(2-phenyl-quinazolin-4-yl)-malonic acid dibenzyl ester (1.00 g, 2.04 mmol), prepared as in Part A, in tetrahydrofuran (20 ml) at 0°C under argon. Then, benzyl-(2-chloro-ethyl)-methyl-amine hydrochloride (450.6 mg, 2.04 mmol) is added and the solution is heated at reflux for 19 h. The solution is cooled, saturated sodium carbonate is added, and the mixture is extracted with ethyl acetate. The combined organic layers are dried with magnesium sulfate and concentrated. The

residue is purified by silica gel chromatography using ethyl acetate:hexanes (3:7) as eluant to give 2-[2-(benzyl-methyl-amino)-ethyl]-2-(2-phenyl-quinazolin-4-yl)-malonic acid dibenzyl ester (840.7 mg):
^{1}H NMR ($CDCl_3$) δ 8.69-8.67 (m, 2H), 8.19 (d, 1H, J = 8 Hz), 7.91-7.82 (m, 2H), 7.61-7.59 (m, 3H), 7.50-7.49 (m, 1H), 7.46-7.18 (m, 15H), 5.28 (s, 4H), 3.47 (s, 2H), 3.05 (t, 2H, J = 7 Hz), 2.61 (t, 2H, J = 7 Hz), 2.17 (s, 3H);
FAB MS *m/z* found 636 (MH^+).

C. Methyl-[3-(2-phenyl-quinazolin-4-yl)-propyl]-amine

Ammonium formate (823.8 mg, 13.06 mmol) is added to a solution of 2-[2-(benzyl-methyl-amino)-ethyl]-2-(2-phenyl-quinazolin-4-yl)-malonic acid dibenzyl ester (830.5 mg, 1.31 mmol), prepared as in Part B, in methanol (13 ml) under argon. Then, 10% palladium on carbon (830.5 mg, 100wt%) is added and the solution is heated at reflux for 42 h. The solution is purged with nitrogen, filtered through Celite®, and concentrated. The residue is purified by silica gel chromatography using methanol:ethyl acetate (2:3) containing 1% ammonium hydroxide as eluant to give the title compound (93.9 mg):
^{1}H NMR (CD_3OD) δ 8.52 (m, 2H), 8.17 (d, 1H, J = 8 Hz), 7.98 (d, 1H, J = 8 Hz), 7.86 (t, 1H, J = 8 Hz), 7.59 (t, 1H, J = 8 Hz), 7.49-7.47 (m, 3H), 3.35 (t, 2H, J = 7 Hz), 2.79 (t, 2H, J = 7 Hz), 2.44 (s, 3H), 2.22-2.16 (m, 2H);
FAB MS *m/z* found 278 (MH^+).

Intermediate 11

Methyl-(2-phenyl-quinazolin-4-yl)-pyrrolidin-3-yl-amine

A. (1-Benzyl-pyrrolidin-3-yl)-methyl-(2-phenyl-quinazolin-4-yl)-amine

Triethylamine (1.24 ml, 8.89 mmol) is added to a solution of (1-benzyl-pyrrolidin-3-yl)-methyl-amine (423.2 mg, 2.22 mmol, Di Cesare, P.*et al, J. Med. Chem.* 1992, *35*, 4205.) in tetrahydrofuran (22 ml). Then, 4-chloro-2-phenyl-quinazoline (535.3 mg, 2.22 mmol) is added to the reaction and the solution is

heated at reflux for 17 h. The solution is concentrated, saturated sodium carbonate is added, and the mixture is extracted with ethyl acetate. The combined organic layers are dried with magnesium sulfate and concentrated. The residue is purified by silica gel chromatography using ethyl acetate:hexanes (3:7) as eluant to give (1-benzyl-pyrrolidin-3-yl)-methyl-(2-phenyl-quinazolin-4-yl)-amine (863.4 mg):
^{1}H NMR ($CDCl_3$) δ 8.55 (m, 2H), 7.93 (d, 2H, J = 8 Hz), 7.68 (t, 1H, J = 7 Hz), 7.52-7.43 (m, 3H), 7.39-7.27 (m, 6H), 5.29 (m, 1H), 3.67 (ABq, 2H, J_{AB} = 13 Hz, $\Delta\nu_{AB}$ = 55 Hz), 3.42 (s, 3H), 2.98-2.90 (m, 2H), 2.76 (t, 1H, J = 9 Hz), 2.47 (t, 2H, J = 7 Hz), 2.09-2.05 (m, 1H);
FAB MS *m/z* found 395 (MH^+).

B. Methyl-(2-phenyl-quinazolin-4-yl)-pyrrolidin-3-yl-amine

Ammonium formate (673.2 mg, 10.67 mmol) is added to a solution of (1-benzyl-pyrrolidin-3-yl)-methyl-(2-phenyl-quinazolin-4-yl)-amine (842.4 mg, 2.13 mmol), prepared as in Part A, in methanol (21 ml) under argon. Then, 10% palladium on carbon (421.2 mg, 50wt%) is added and the solution is heated at reflux for 14 h. The solution is purged with nitrogen, filtered through Celite®, and concentrated. The residue is purified by silica gel chromatography using methanol:ethyl acetate (1:9) containing 1% ammonium hydroxide as eluant to give the title compound (161.9 mg):
^{1}H NMR (CD_3OD) δ 8.32 (dd, 2H, J = 6, 2 Hz), 7.99 (d, 1H, J = 8 Hz), 7.72 (d, 1H, J = 8 Hz), 7.59 (t, 1H, J = 8 Hz), 7.40-7.38 (m, 3H), 7.25 (t, 1H, J = 7 Hz), 3.98-3.93 (m, 2H), 3.80-3.73 (m, 1H), 3.70-3.65 (m, 1H), 3.28-3.22 (m, 1H), 2.37 (s, 3H), 2.15-2.06 (m, 1H), 1.87-1.80 (m, 1H);
FAB MS *m/z* found 305 (MH^+).

Intermediate 12

(3-Methyl-pyrrolidin-3-yl)-(2-phenyl-quinazolin-4-yl)-amine

A. 1-Benzyl-3-methyl-pyrrolidine-3-carboxylic acid benzyl ester

Benzyl 2-methyl-2-propenoate (5.00 g, 28.38 mmol) is added to a solution of benzyl-methoxymethyl-trimethylsilanylmethyl-amine (10.11 g, 42.56 mmol, Terao, Y.*et al, Chem. Pharm. Bull.* 1985, *33*, 2762.) in dichloromethane (57 ml) at 0°C. Then, trifluoroacetic acid (0.22 ml, 2.84 mmol) is added to the reaction and the solution is stirred for 1 h. Saturated sodium carbonate is added, and the mixture is extracted with dichloromethane. The combined organic layers are dried with magnesium sulfate and concentrated. The residue is purified by silica gel chromatography using ether:dichloromethane (1:9) as eluant to give 1-benzyl-3-methyl-pyrrolidine-3-carboxylic acid benzyl ester (7.84 g):
^{1}H NMR ($CDCl_3$) δ 7.38-7.22 (m, 10H), 5.14 (s, 2H), 3.61 (ABq, 2H, J_{AB} = 13 Hz, $\Delta\nu_{AB}$ = 9 Hz), 3.01 (d, 1H, J = 9 Hz), 2.68-2.63 (m, 2H), 2.49-2.39 (m, 2H), 1.71-1.64 (m, 1H), 1.37 (s, 3H);
FAB MS *m/z* found 310 (MH^+).

B. 1-Benzyl-3-methyl-pyrrolidine-3-carboxylic acid

10% Palladium on carbon (294 mg, 10 wt%) is added to a solution of 1-benzyl-3-methyl-pyrrolidine-3-carboxylic acid benzyl ester (2.94 g, 9.50 mmol), prepared as in Part A, in methanol (24 ml) under argon. Then, the reaction is fitted with an hydrogen balloon and the flask is repeatedly evacuated and purged with hydrogen to remove all argon and stirred for 3 h. The solution is purged with nitrogen, filtered through Celite®, and concentrated to give 1-benzyl-3-methyl-pyrrolidine-3-carboxylic acid (1.81g):
^{1}H NMR (CD_3OD) δ 7.51-7.33 (m, 5H), 4.22 (ABq, 2H, J_{AB} = 13 Hz, $\Delta\nu_{AB}$ = 15 Hz), 3.65 (d, 1H, J = 11 Hz), 3.34-3.20 (m, 2H), 2.84 (d, 1H J = 11 Hz), 2.52-2.45 (m, 1H), 1.88-1.76 (m, 1H), 1.33 (s, 3H);
FAB MS *m/z* found 220 (MH^+).

C. 1-Benzyl-3-methyl-3-(1,1-dimethyl-ethyl-oxy-carbonyl-amino)-pyrrolidine

Triethylamine (2.82 g, 27.87 mmol) is added to 1-benzyl-3-methyl-pyrrolidine-3-carboxylic acid (5.56 g, 25.34 mmol), prepared as in Part B, in *tert*-butanol:N,N-dimethylformamide (4:1, 127 ml). Then, diphenylphosphoryl azide (6.01 ml, 27.87

mmol) is added to the mixture and it is heated at 100°C for 63 h. The solution is concentrated, saturated sodium carbonate is added, and the mixture is extracted with ethyl acetate. The combined organic layers are dried with magnesium sulfate and concentrated. The residue is purified by silica gel chromatography using ethyl acetate:hexanes (3:2) as eluant to give 1-benzyl-3-methyl-3-(1,1-dimethyl-ethyl-oxy-carbonyl-amino)-pyrrolidine (1.49 g):
^{1}H NMR ($CDCl_3$) δ 7.29-7.20 (m, 5H), 4.72 (br s, 1H), 3.59 (ABq, 2H, J_{AB} = 13 Hz, $\Delta\nu_{AB}$ = 18 Hz), 2.77-2.69 (m, 2H), 2.60-2.52 (m, 1H), 2.46 (d, 1H, J = 10 Hz), 2.07-1.99 (m, 1H), 1.87-1.78 (m, 1H), 1.43 (s, 3H), 1.41 (s, 9H);
FAB MS *m/z* found 291 (MH^+).

D. 1-Benzyl-3-methyl-pyrrolidin-3-yl-amine

Trifluoroacetic acid:water:anisole (8:1:1, 13 ml) is added to the 1-benzyl-3-methyl-3-(1,1-dimethyl-ethyl-oxy-carbonyl-amino)-pyrrolidine (1.49 g, 5.13 mmol), prepared as in Part C, and the reaction is stirred for 14 h. The solution is concentrated, saturated sodium carbonate is added, and the mixture is extracted with ethyl acetate. The combined organic layers are dried with magnesium sulfate and concentrated to give 1-benzyl-3-methyl-pyrrolidin-3-yl-amine (866.4 mg):
^{1}H NMR (CD_3OD) δ 7.32-7.21 (m, 5H), 3.60 (s, 2H), 2.85-2.78 (m, 1H), 2.55-2.47 (m, 1H), 2.45 (ABq, 2H, J_{AB} = 10 Hz, $\Delta\nu_{AB}$ = 41 Hz), 1.88-1.68 (m, 2H), 1.24 (s, 3H);
FAB MS *m/z* found 191 (MH^+).

E. (1-Benzyl-3-methyl-pyrrolidin-3-yl)-(2-phenyl-quinazolin-4-yl)-amine

N,N-Di-*iso*-propyl-ethyl-amine (0.94 ml, 5.39 mmol) is added to a solution of 1-benzyl-3-methyl-pyrrolidin-3-yl-amine (256.5 mg, 1.35 mmol), prepared as in Part D, in ethanol (4.5 ml). Then, 4-chloro-2-phenyl-quinazoline (324.4 mg, 1.35 mmol) is added to the reaction and the solution is heated in a sealed tube at 150°C for 63 h. The solution is concentrated, saturated sodium carbonate is added, and the mixture is extracted with ethyl acetate. The combined organic layers are dried with magnesium sulfate and concentrated. The residue is purified by silica gel

chromatography using ethyl acetate as eluant to give (1-benzyl-3-methyl-pyrrolidin-3-yl)-(2-phenyl-quinazolin-4-yl)-amine (520.8 mg):
^{1}H NMR ($CDCl_3$) δ 8.53 (dd, 2H, J = 8, 2 Hz), 7.90 (d, 1H, J = 8 Hz), 7.72-7.67 (m, 2H), 7.51-7.46 (m, 3H), 7.42-7.25 (m, 6H), 5.94 (s, 1H), 3.69 (ABq, 2H, J_{AB} = 13 Hz, $\Delta\nu_{AB}$ = 10 Hz), 3.14 (d, 1H, J = 10 Hz), 2.85 (ABq, 2H, J_{AB} = 7 Hz, $\Delta\nu_{AB}$ = 15 Hz), 2.69-2.63 (m, 1H), 2.55-2.47 (m, 1H), 2.22-2.15 (m, 1H), 1.84 (s, 3H); FAB MS *m/z* found 395 (MH^+).

F. (3-Methyl-pyrrolidin-3-yl)-(2-phenyl-quinazolin-4-yl)-amine

Ammonium formate (416.2 mg, 6.60 mmol) is added to a solution of (1-benzyl-3-methyl-pyrrolidin-3-yl)-(2-phenyl-quinazolin-4-yl)-amine (520.8 mg, 1.32 mmol), prepared as in Part E, in methanol (26 ml) under argon. Then, 10% palladium on carbon (130.2 mg, 25wt%) is added and the solution is heated at reflux for 28 h. The solution is purged with nitrogen, filtered through Celite®, and concentrated. The residue is purified by silica gel chromatography using methanol:ethyl acetate (3:2) containing 1% ammonium hydroxide as eluant to give the title compound (380.7 mg):
^{1}H NMR (CD_3OD) δ 8.36 (dd, 2H, J = 8, 4 Hz), 8.17 (d, 1H, J = 8 Hz), 7.80 (d, 1H, J = 8 Hz), 7.72 (dt, 1H, J = 7, 1 Hz), 7.51-7.41 (m, 4H), 3.65 (d, 1H, J = 12 Hz), 3.18-3.00 (m, 3H), 2.62-2.53 (m, 1H), 2.11-2.02 (m, 1H), 1.75 (s, 3H);
FAB MS *m/z* found 305 (MH^+).

Intermediate 13

(3,4-Dimethyl-pyrrolidin-3-yl)-(2-phenyl-quinazolin-4-yl)-amine

A. 1-Benzyl-3,4-dimethyl-pyrrolidine-3-carboxylic acid benzyl ester

Benzyl 2-methyl-2-butenoate (3.00 g, 15.77 mmol) is added to a solution of benzyl-methoxymethyl-trimethylsilanylmethyl-amine (5.62 g, 23.65 mmol) in dichloromethane (32 ml) at 0°C. Then, trifluoroacetic acid (0.12 ml, 1.58 mmol) is added to the reaction and the solution is stirred for 1 h. Saturated sodium carbonate

is added, and the mixture is extracted with dichloromethane. The combined organic layers are dried with magnesium sulfate and concentrated. The residue is purified by silica gel chromatography using ether:dichloromethane (1:9) as eluant to give 1-benzyl-3,4-dimethyl-pyrrolidine-3-carboxylic acid benzyl ester (3.39 g):
^{1}H NMR ($CDCl_3$) δ 7.36-7.21 (m, 10H), 5.12 (s, 2H), 3.62 (ABq, 2H, J_{AB} = 13 Hz, $\Delta\nu_{AB}$ = 37 Hz), 3.36 (d, 1H, J = 9 Hz), 2.95 (t, 1H, J = 8 Hz), 2.70 (h, 1H, J = 8 Hz), 2.35-2.16 (m, 2H), 1.21 (s, 3H), 0.98 (d, 3H, J = 7 Hz);
FAB MS *m/z* found 324 (MH^+).

B. 1-Benzyl-3,4-dimethyl-pyrrolidine-3-carboxylic acid

10% Palladium on carbon (339 mg, 10 wt%) is added to a solution of 1-benzyl-3,4-dimethyl-pyrrolidine-3-carboxylic acid benzyl ester (3.39 g, 10.48 mmol), prepared as in Part A, in methanol (26 ml) under argon. Then, the reaction is fitted with an hydrogen balloon and the flask is repeatedly evacuated and purged with hydrogen to remove all argon and stirred for 90 min. The solution is purged with nitrogen, filtered through Celite®, and concentrated to give 1-benzyl-3,4-dimethyl-pyrrolidine-3-carboxylic acid:
^{1}H NMR (CD_3OD) δ 7.54-7.52 (m, 2H), 7.46-7.43 (m, 3H), 4.35 (ABq, 2H, J_{AB} = 13 Hz, $\Delta\nu_{AB}$ = 15 Hz), 3.86 (d, 1H, J = 12 Hz), 3.56 (t, 1H, J = 7 Hz), 3.07-2.96 (m, 2H), 2.76-2.70 (m, 1H), 1.22 (s, 3H), 1.07 (d, 3H, J = 7 Hz);
FAB MS *m/z* found 234 (MH^+).

C. 1-Benzyl-3,4-dimethyl-3-(methyl-oxy-carbonyl-amino)-pyrrolidine

Triethylamine (1.61 g, 11.53 mmol) is added to 1-benzyl-3,4-dimethyl-pyrrolidine-3-carboxylic acid (10.48 mmol carried forward from above), prepared as in Part B, in methanol:N,N-dimethylformamide (4:1, 50 ml). Then, diphenylphosphoryl azide (2.48 ml, 11.53 mmol) is added to the mixture and it is heated at reflux for 14 h. The solution is concentrated, saturated sodium carbonate is added, and the mixture is extracted with ethyl acetate. The combined organic layers are dried with magnesium sulfate and concentrated. The residue is purified

by silica gel chromatography using ethyl acetate:hexanes (3:2) as eluant to give 1-benzyl-3,4-dimethyl-3-(methyl-oxy-carbonyl-amino)-pyrrolidine (0.81 g):
^{1}H NMR ($CDCl_3$) δ 7.29-7.20 (m, 5H), 5.03 (br s, 1H), 3.59 (s, 3H), 3.56 (ABq, 2H, J_{AB} = 13 Hz, $\Delta\nu_{AB}$ = 30 Hz), 3.08 (t, 1H, J = 9 Hz), 2.90 (d, 1H, J = 10 Hz), 2.36 (d, 1H, J = 10 Hz), 2.31 (q, 1H, J = 8 Hz), 2.03-1.99 (m, 1H), 1.30 (s, 3H), 0.96 (d, 3H, J = 7 Hz);
FAB MS *m/z* found 263 (MH^+).

D. 1-Benzyl-3,4-dimethyl-pyrrolidin-3-yl-amine

Potassium hydroxide (1.54 g, 27.44 mmol) is added to the 1-benzyl-3,4-dimethyl-3-(methyl-oxy-carbonyl-amino)-pyrrolidine (0.72 g, 2.74 mmol), prepared as in Part C, in ethanol:water (27 ml, 1:1) and the reaction is heated at reflux for 67 h. The solution is cooled and the mixture is extracted with ethyl acetate. The combined organic layers are dried with magnesium sulfate and concentrated. The residue is purified by silica gel chromatography using methanol:ethyl acetate (1:9) containing 1% ammonium hydroxide as eluant to give 1-benzyl-3,4-dimethyl-pyrrolidin-3-yl-amine (429.6 mg):
^{1}H NMR (CD_3OD) δ 7.33-7.22 (m, 5H), 3.58 (ABq, 2H, J_{AB} = 13 Hz, $\Delta\nu_{AB}$ = 14 Hz), 3.07 (t, 1H, J = 7 Hz), 2.51 (ABq, 2H, J_{AB} = 20 Hz, $\Delta\nu_{AB}$ = 157 Hz), 2.07-1.95 (m, 2H), 1.07 (s, 3H), 0.93 (d, 3H, J = 9 Hz);
FAB MS *m/z* found 205 (MH^+).

E. (1-Benzyl-3,4-dimethyl-pyrrolidin-3-yl)-(2-phenyl-quinazolin-4-yl)-amine

N,N-Di-*iso*-propyl-ethyl-amine (1.36 ml, 7.77 mmol) is added to a solution of 1-benzyl-3,4-dimethyl-pyrrolidin-3-yl-amine (396.8 mg, 1.94 mmol), prepared as in Part D, in ethanol (6.5 ml). Then, 4-chloro-2-phenyl-quinazoline (467.4 mg, 1.94 mmol) is added to the reaction and the solution is heated in a sealed tube at 150°C for 16 h. The solution is concentrated, saturated sodium carbonate is added, and the mixture is extracted with ethyl acetate. The combined organic layers are dried with magnesium sulfate and concentrated. The residue is purified by silica gel

chromatography using ethyl acetate as eluant to give (1-benzyl-3,4-dimethyl-pyrrolidin-3-yl)-(2-phenyl-quinazolin-4-yl)-amine (740.3 mg):
^{1}H NMR ($CDCl_3$) δ 8.55-8.53 (m, 2H), 7.90 (d, 1H, *J* = 8 Hz), 7.69 (d, 1H, *J* = 8 Hz), 7.49-7.26 (m, 10H), 6.10 (s, 1H), 3.70 (s, 2H), 3.31 (d, 1H, *J* = 10 Hz), 3.21 (t, 1H, *J* = 9 Hz), 2.78 (q, 1H, *J* = 7 Hz), 2.70 (d, 1H, *J* = 10 Hz), 2.11 (t, 1H, *J* = 8 Hz), 1.72 (s, 3H), 1.18 (d, 3H, *J* = 7 Hz);
FAB MS *m/z* found 409 (MH^+).

F. (3,4-Dimethyl-pyrrolidin-3-yl)-(2-phenyl-quinazolin-4-yl)-amin

Ammonium formate (114.3 mg, 18.12 mmol) is added to a solution of (1-benzyl-3,4-dimethyl-pyrrolidin-3-yl)-(2-phenyl-quinazolin-4-yl)-amine (740.3 mg, 1.81 mmol), prepared as in Part E, in methanol (18 ml) under argon. Then, 10% palladium on carbon (370.1 mg, 50wt%) is added and the solution is heated at reflux for 15 h. The solution is purged with nitrogen, filtered through Celite®, and concentrated. The residue is purified by silica gel chromatography using methanol:ethyl acetate (1:1) containing 1% ammonium hydroxide as eluant to give the title compound (430.4 mg):
^{1}H NMR (CD_3OD) δ 8.36-8.33 (m, 2H), 8.21 (d, 1H, *J* = 8 Hz), 7.83-7.72 (m, 2H), 7.49-7.41 (m, 4H), 3.65 (d, 1H, *J* = 12 Hz), 3.30-3.23 (m, 2H), 2.83 (q, 1H, *J* = 8 Hz), 2.61 (dd, 1H, *J* = 11, 8 Hz), 1.64 (s, 3H), 1.15 (d, 3H, *J* = 7 Hz);
FAB MS *m/z* found 319 (MH^+).

Intermediate 14

4-(2,5-Dimethyl-piperazin-1-yl)-2-phenyl-quinazoline

4-Chloro-2-phenyl-quinazoline (5.00 g, 20.77 mmol) in tetrahydrofuran (100 ml) is added dropwise over 20 minutes to a stirred solution of trans-2,5-dimethyl-piperazine (11.65 g, 103.87 mmol) in tetrahydrofuran (100 ml) and the solution is heated to reflux for 48 h. Saturated sodium carbonate is added and the reaction extracted with ethyl acetate. The combined organic layers are dried with magnesium sulfate and concentrated. The residue is purified by silica gel

chromatography using methanol:ethyl acetate (5:95) containing 1% ammonium hydroxide as eluant to give the title compound (4.16 g): ^{1}H NMR ($CDCl_3$) δ 8.57 (d, 2H, *J* = 7.4 Hz), 7.88 (m, 2H), 7.53 (t, 1H, *J* = 7.6 Hz), 7.35 (m, 3H), 7.22 (t, 1H, *J* = 7.5 Hz), 3.75 (m, 1H), 3.42 (d, 1H, *J* = 11.0 Hz), 2.99 (m, 2H), 2.64 (m, 2H), 1.46 (s, 1H, 1.13 (d, 3H, *J* = 5.9 Hz), 0.84 (d, 3H, *J* = 6.1 Hz);
FAB MS *m/z* found 319 (MH^+).

Intermediate 15

5-[2-(4-Amino-cyclohexylamino)-ethyl]-2-methoxy-benzenesulfonamide

5-(2-Chloro-ethyl)-2-methoxy-benzenesulfonamide (0.87 g, 3.5 mmol) is added to a stirred solution of 1,4-diaminocyclohexane (2.00 g, 17.51 mmol), potassium carbonate (0.97 g, 7.00 mmol), and sodium iodide (0.05 g, 0.35 mmol) in 1,4-dioxane (35 ml) and the solution set to reflux for 48 h. Saturated sodium carbonate is added and the reaction extracted with ethyl acetate. The combined layers are dried with magnesium sulfate and concentated. The residue is purified by silica gel chromatography using methanol:ethyl acetate (gradient of 1:1 to 1:0) containing 1% ammonium hydroxide as eluant to give the title compound (180.0 mg): ^{1}H NMR (CD_3OD) δ 7.72 (s, 1H), 7.43 (d, 1H, *J* = 8.6 Hz), 7.13 (d, 1H, *J* = 8.6 Hz), 3.95 (s, 3H), 3.34 (s, 2H), 2.87 (br s, 1H), 2.78 (s, 4H), 2.62 (br s, 1H), 1.54 (m, 6H);
FAB MS *m/z* found 328.1 (MH^+).

Intermediate 16

(R)-5-[2-(3-Amino-pyrrolidin-1-yl)-ethyl]-2-methoxy-benzenesulfonamide

Synthesized in a manner similar to Intermediate 15, using 5-(2-Chloro-ethyl)-2-methoxy-benzenesulfonamide (5.00g, 20.02 mmol) and (R)-3-Aminopyrrolidine dihydrochloride (15.92 g, 100.11 mmol) to give the title compound (0.52 g): ^{1}H NMR (CD_3OD) δ 7.70 (s, 1H), 7.42 (d, 1H, *J* = 8.3 Hz), 7.12 (d, 1H, *J* = 8.3 Hz), 3.95 (s, 3H), 3.47 (m, 1H), 2.75 (m, 7H), 2.36 (m, 1H), 2.19 (m, 1H), 1.55 (m, 1H);
FAB MS *m/z* found 300.08 (MH^+).

Intermediate 17

(R)-1-(2-phenyl-quinazolin-4-yl)-pyrrolidin-3-ylamine

4-chloro-2-phenyl quinazoline (2.42 g, 10.06 mmol) is added to a stirred solution of (R)-3-aminopyrrolidine dihydrochloride (8.00 g, 50.30 mmol) and triethylamine (14 ml, 100.60 mmol) in tetrahydrofuran (100 ml) and the solution heated to reflux over 16 h. The solution is concentrated, saturated sodium carbonate added, and the reaction extracted with ethyl acetate. The combined layers are dried with magnesium sulfate and concentrated. The residue is purified by silica gel chromatography using methanol:ethyl acetate (1:9) containing 1% ammonium hydroxide as eluant to give the title compound (2.04g):
^{1}H NMR (CD_3OD) δ 8.27 (m, 2H), 7.78 (d, 1H, J = 8.6 Hz), 7.64 (d, 1H, J = 8.3 Hz), 7.48 (m, 1H), 7.34 (m, 3H), 7.09 (m, 1H), 3.73 (m, 2H), 3.55 (m, 1H), 3.33 (m, 2H), 1.90 (m, 1H), 1.55 (m, 1H); [1]
FAB MS *m/z* found 291.2 (MH^+).

Intermediate 18

(S)-5-[2-(3-Amino-pyrrolidin-1-yl)-ethyl]-2-methoxy-benzenesulfonamide

Synthesized in a manner similar to Intermediate 15, using 5-(2-Chloro-ethyl)-2-methoxy-benzenesulfonamide (5.00 g, 20.02 mmol) and (S)-3-Aminopyrrolidine dihydrochloride (15.92 g, 100.11 mmol) to give the title compound (0.14 g):
^{1}H NMR (CD_3OD) δ 7.61 (s, 1H), 7.34 (d, 1H, J = 8.6 Hz), 7.03 (d, 1H, J = 8.6 Hz), 3.86 (s, 3H), 3.37 (m, 1H), 3.21 (m, 1H), 2.69 (m, 6H), 2.27 (m, 1H), 2.10 (m, 1H), 1.45 (m, 1H);
^{13}C NMR (CD_3OD) δ 156.2, 135.4, 133.1, 131.6, 128.9, 113.6, 62.7, 58.7, 56.7, 53.9, 51.2, 34.6, 33.9.

Intermediate 19

(S)-1-(2-phenyl-quinazolin-4-yl)-pyrrolidin-3-ylamine

Synthesized in a manner similar to Intermediate 17, using 4-Chloro-2-phenyl quinazoline (5.00 g, 20.77 mmol) and (S)-3-Aminopyrrolidine dihydrochloride (9.91 g, 62.32 mmol) and triethylamine (17.5 ml, 124.64 mmol) to give the title compound (5.28 g):

^{1}H NMR (CD_3OD) δ 8.36-8.33 (m, 2H), 7.99-7.96 (d, 1H, J = 8.4 Hz), 7.75-7.72 (d, 1H, J = 8.3 Hz), 7.62-7.57 (m, 1H), 7.42-7.40 (m, 3H), 7.25-7.21 (m, 1H), 3.96-3.89 (m, 2H), 3.79-3.73 (m, 1H), 3.54-3.45 (m, 2H), 2.08-2.02 (m, 1H), 1.74-1.68 (m, 1H); FAB MS *m/z* found 291 (MH^+).

Intermediate 20

4-(2,5-diaza-bicyclo[2.2.1]hept-2-yl)-2-phenyl-quinazoline

Synthesized in a manner similar to Intermediate 17, using 4-Chloro-2-phenyl quinazoline (0.14 g, 1.38 mmol) and 2,5-Diaza-bicyclo[2.2.1]heptane (1.00 g, 4.15 mmol, Bouzard, D., *et al, J. Med. Chem.*; 1990; 33(5); 1344-1352) to give the title compound (170.0 mg):

^{1}H NMR (CD_3OD) δ 8.39-8.35 (m, 2H), 8.04-8.01 (d, 1H, J = 8.1 Hz), 7.83-7.82 (m, 1H), 7.80-7.67 (m, 1H)m 7.47-7.35 (m, 4H), 5.28 (s, 1H), 4.21-4.17 (dd, 1H, J = 9.8, 2.2 Hz), 3.86 (s, 1H), 3.75-3.72 (dd, 1H, J = 9.8, 1.2 Hz), 3.31-3.29 (dd, 1H, J = 4.9, 1.7 Hz), 3.13-3.09 (dd, 1H, J = 10.3, 2.0 Hz), 2.03-1.83 (AB_q, 2H, J_{AB} = 10.0 Hz, $\Delta\upsilon_{AB}$ = 48.3 Hz);

FAB MS *m/z* found 303 (MH^+).

Intermediate 21

N-methyl-N-(2-phenyl-quinazolin-4-yl)-ethane-1,2-diamine

Synthesized in a manner similar to Intermediate 17, using 4-Chloro-2-phenyl quinazoline (6.49 g, 27.0 mmol) and N-methyl ethylene diamine (12.0 ml, 134.0 mmol) to give the title compound(7.0 g):

^{1}H NMR ($CDCl_3$) δ 8.53-8.50 (m, 2H), 7.88-7.82 (m, 2H), 7.66-7.60 (m, 1H), 7.49-7.43 (m, 3H), 7.33-7.27 (m, 1H), 7.03 (br s, 1H), 3.81-3.79 (dd, 2H), 2.91-2.88 (dd, 2H), 2.40 (s, 3H);

FAB MS *m/z* found 279 (MH^+).

Intermediate 22

5-[2-[(2-Mercapto-ethyl)-methyl-amino]-ethyl]-2-methoxy-benzenesulfonamide

A. N-(2-Mercapto-ethyl)-formamide

Cysteamine (10.0g, 129.62 mmol) and ethyl formate (173 ml, 0.75 M) are heated to reflux as a neat solution for 16 h. The solution is concentrated and the residue purified by silica gel chromatography using methanol:ethyl acetate (1:9) as eluant to give N-(2-mercapto-ethyl)-formamide (9.56 g, 70%):
^{1}H NMR ($CDCl_3$) δ 8.21(s, 1H), 6.41-6.40 (br s, 1H), 3.53-3.41 (m, 2H), 2.74-2.64 (m, 2H), 1.46-1.40 (t, 1H, J = 8.6 Hz);
FAB MS *m/z* 106 (MH^+).

B. 2-Methylamino-ethanethiol

Borane tetrahydrofuran complex (1M, 182 ml, 181.82 mmol) is added to a stirred solution of N-(2-Mercapto-ethyl)-formamide, prepared as in Part A, in tetrahydrofuran (300 ml) at 0°C over 45 mins. The solution is warmed to room temperature and then heated to reflux over 24 h. The solution is cooled to 0°C and the reaction quenched with methanol (150 ml). The solution is then heated to reflux for 1 hr. The solution is concentrated and a short path distillation performed at 1.5 atm (25°C to 150°C temperature gradient). The compound condensed from the gaseous phase as a white solid and had to be scraped from the condenser to obtain 2-methylamino-ethanethiol (0.24 g):
^{1}H NMR (CD_3OD) δ 2.78-2.73 (t, 2H), 2.61-2.59 (t, 2H), 2.39 (s, 3H);
CI (NH_3) MS *m/z* found 91 (M^+).

C. 5-[2-[(2-Mercapto-ethyl)-methyl-amino]-ethyl]-2-methoxy-benzenesulfonamide

5-(2-Chloro-ethyl)-2-methoxy-benzenesulfonamide (0.66 g, 2.63 mmol) is added to a stirred solution of 2-Methylamino-ethanethiol (0.24 g, 2.63 mmol),

prepared as in Part B, potassium carbonate (0.73 g, 5.26 mmol), and sodium iodide (0.39 g, 2.63 mmol) in 1,4-dioxane (25 ml) and the solution heated to reflux for 16 h. Saturated sodium carbonate is added and the reaction extracted with ethyl acetate. The combined layers are dried with magnesium sulfate and concentrated. The residue is purified by silica gel chromatography using methanol:ethyl acetate (1:1) containing 1% ammonium hydroxide as eluant to give the title compound (220.0 mg):
^{1}H NMR (CD_3OD) δ 7.71-7.70 (d, 1H, J = 2.2 Hz), 7.43-7.42 (dd, 1H, J = 2.2 Hz), 7.13-7.10 (d, 1H, J = 8.3 Hz), 3.95 (s, 3H), 2.88-2.65 (m, 8H), 2.39 (s, 3H);
FAB MS *m/z* found 305 (MH^+).

Intermediate 23

2-Phenyl-4-(pyrrolidin-3-yloxy)-quinazoline

A. 4-(1-benzyl-pyrrolidin-3-yloxy)-2-phenyl-quinazoline

4-Chloro-2-phenyl quinazoline (6.79 g, 28.21 mmol) is added to a stirred solution of (S)-(-)-1-benzyl-3-pyrrolidinol (5.00 g, 28.21 mmol) and sodium hydride (60% suspension, 1.35 g, 33.85 mmol) in tetrahydrofuran and the solution heated to reflux for 16 h. The reaction is quenched with water:tetrahydrofuran (1:1). Saturated sodium carbonate is added and the reaction extracted with ethyl acetate. The combined layers are dried with magnesium sulfate and concentrated. The residue is purified by silica gel chromatography using methanol:ethyl acetate (5:95) containing 1% ammonium hydroxide as eluant to give 4-(1-benzyl-pyrrolidin-3-yloxy)-2-phenyl-quinazoline (9.03 g, 84%):
^{1}H NMR ($CDCl_3$) δ 8.57-8.54 (m, 2H), 8.18-8.16 (d, 1H, J = 8.1 Hz), 7.99-7.96 (d, 1H, J = 8.5 Hz), 7.83-7.78 (m, 1H), 7.53-7.48 (m, 4H), 7.39-7.23 (m, 5H), 5.90-5.87 (m, 1H), 3.79-3.66 (q, 2H, J = 12.7 Hz), 3.25-3.19 (dd, 1H, J = 10.7, 6.6 Hz), 2.95-2.85 (m, 2H), 2.67-2.55 (m, 2H), 2.18-2.17 (m, 1H);
FAB MS *m/z* found 382 (MH^+).

B. 2-Phenyl-4-(pyrrolidin-3-yloxy)-quinazoline

Ammonium formate (1.65 g, 26.21 mmol) is added to a solution of 4-(1-benzyl-pyrrolidin-3-yloxy)-2-phenyl-quinazoline (2.00 g, 5.24 mmol), prepared as in Part A, in methanol (52 ml) under argon. Then, 5% palladium on carbon (1.00g, 25 wt%) is added and the solution is heated at reflux for 2 h. The solution is purged with nitrogen, filtered through Celite®, and concentrated. The residue is purified by silica gel chromatography using methanol:ethyl acetate (gradient of 1:9 to 1:3) containing 1% ammonium hydroxide to give the title compound (1.01 g):
^{1}H NMR ($CDCl_3$) δ 8.57-8.53 (m, 2H), 8.08-8.05 (dd, 1H, J = 8.3, 0.8 Hz), 7.95-7.93 (d, 2H, J = 8.3 Hz), 7.77-7.71 (m, 1H), 7.51-7.40 (m, 4H), 5.86-5.83 (m, 1H), 3.35-3.33 (m, 3H), 3.25-3.21 (m, 1H), 3.04-3.03 (m, 1H), 2.30-2.25 (m, 1H), 2.16-2.05 (m, 1H);
FAB MS *m/z* found 292 (MH^+).

Intermediate 24

(2S,4S)-(2-Methyl-pyrrolidin-4-yl)-(2-phenyl-quinazolin-4-yl)-amine

A. (2S,4S)-[2-methyl-1-(toluene-4-sulfonyl)-pyrrolidin-4-yl]-(2-phenyl-quinazolin-4-yl)-amine

Synthesized in a manner similar to Intermediate 17, using 4-Chloro-2-phenyl quinazoline (0.07 g, 0.29 mmol) and (2S, 4S)-2-Methyl-1-(toluene-4-sulfonyl)-pyrrolidin-4-ylamine (0.07 g, 0.29 mmol; Di Cesare, P.*et al, J. Med. Chem.*; 1992; 35(22); 4205-4213.) to give (2S, 4S)-[2-methyl-1-(toluene-4-sulfonyl)-pyrrolidin-4-yl]-(2-phenyl-quinazolin-4-yl)-amine (0.08 g):
^{1}H NMR ($DCDl_3$) δ 8.53-8.50 (m, 2H), 7.92-7.89 (d, 1H, J = 8.3 Hz), 7.72-7.69 (d, 2H, J = 8.0 Hz), 7.59-7.48 (m, 4H), 7.36-7.33 (m, 2H), 7.12-7.09 (d, 2H, J = 8.1 Hz), 5.58-5.57 (m, 1H), 4.78 (m, 1H), 4.05 (m, 1H), 2.36-2.25 (m, 1H), 2.19 (s, 3H), 2.04-2.01(m, 1H), 1.49-1.47 (d, 3H, J = 6.1 Hz), 1.26 (m, 1H);
FAB MS *m/z* found 459 (MH^+).

B. (2S,4S)-(2-Methyl-pyrrolidin-4-yl)-(2-phenyl-quinazolin-4-yl)-amine

Hydrogen bromide (33% solution in acetic acid, 0.42 ml, 1.74 mmol) is added to a stirred solution of (2S, 4S)-[2-methyl-1-(toluene-4-sulfonyl)-pyrrolidin-4-yl]-(2-phenyl-quinazolin-4-yl)-amine (0.32 g, 0.70 mmol), prepared as in Part A, in acetic acid (23 ml) and the solution set to reflux for 16 h. The solution is concentrated and the residue purified by silica gel chromatography using ethyl acetate:methanol (1:4) containing 1% ammonium hydroxide as eluant to give the title compound (90.0 mg):
^{1}H NMR ($CDCl_3$) δ 8.57-8.54 (m, 2H), 7.92-7.89 (d, 1H, J = 8.1 Hz), 7.79-7.76 (d, 1H, J = 8.3 Hz), 7.73-7.68 (t, 1H, J = 7.6 Hz), 7.51-7.45 (m, 3H), 7.42-7.37 (t, 1H, J = 7.5 Hz), 6.10-6.08 (m, 1H), 5.00 (m, 1H), 3.72-3.66 (dd, 1H, J = 11.5, 6.6 Hz), 3.48-3.45 (m, 1H), 2.99-2.94 (dd, 1H, J = 11.5, 4.7 Hz), 2.76 (br s, 1H), 2.09-2.08 (m, 1H), 1.91-1.86 (m, 1H), 1.26-1.24 (d, 3H, J = 6.1 Hz);
FAB MS *m/z* found 305 (MH^+).

Intermediate 25

(2R,4S)-(2-Methyl-pyrrolidin-4-yl)-(2-phenyl-quinazolin-4-yl)-amine

A. (2R,4S)-[2-methyl-1-(toluene-4-sulfonyl)-pyrrolidin-4-yl]-(2-phenyl-quinazolin-4-yl)-amine

Synthesized in a manner similar to Intermediate 17, using 4-Chloro-2-phenyl quinazoline (0.25 g, 1.04 mmol) and (2R, 4S)-2-Methyl-1-(toluene-4-sulfonyl)-pyrrolidin-4-ylamine (0.25 g, 1.00 mmol; Di Cesare, P.*et al*, *J. Med. Chem.*; 1992; 35(22); 4205-4213.) to give (2R, 4S)-[2-methyl-1-(toluene-4-sulfonyl)-pyrrolidin-4-yl]-(2-phenyl-quinazolin-4-yl)-amine (0.37 g):
^{1}H NMR ($DCDl_3$) δ 8.48-8.45 (m, 2H), 7.93-7.90 (m, 1H), 7.83-7.80 (d, 2H, J = 8.1 Hz), 7.73-7.71 (d, 2H, J = 7.3 Hz), 7.59-7.36 (m, 6H), 5.87-5.85 (m, 1H), 4.61-4.58 (m, 1H), 3.85-3.81 (m, 1H), 3.70-3.68 (m, 1H), 3.55-3.49 (m, 1H), 2.45-2.41 (m, 4H), 1.85-1.80 (m, 1H), 1.54-1.52 (d, 3H, J = 6.1 Hz);
FAB MS *m/z* found 459 (MH^+).

B. (2R,4S)-(2-Methyl-pyrrolidin-4-yl)-(2-phenyl-quinazolin-4-yl)-amine

Hydrogen bromide (33% solution in acetic acid, 0.5 ml, 2.02 mmol) is added to a stirred solution of (2R, 4S)-[2-methyl-1-(toluene-4-sulfonyl)-pyrrolidin-4-yl]-(2-phenyl-quinazolin-4-yl)-amine (0.37 g, 0.81 mmol), prepared as in Part A, in acetic acid (27 ml) and the solution set to reflux for 16 h. The solution is concentrated, triturated with acetonitrile:methanol (1:1), and cooled (4°C). A solid precipitated out of the solution to give the title compound (87.6 mg):
^{1}H NMR (CD_3OD) d 8.56-8.53 (d, 1H, J = 8.1 Hz), 8.32-8.29 (m, 2H), 8.04-7.93 (m, 2H), 7.77-7.59 (m, 4H), 5.40-5.35 (m, 1H), 3.94-3.81 (m, 2H), 3.54-3.48 (dd, 1H, J = 12.5, 6.9 Hz), 2.84-2.75 (m, 1H), 2.18-2.07 (m, 1H), 1.51-1.49 (d, 3H, J = 6.6 Hz); FAB MS *m/z* found 305 (MH^+).

Intermediate 26

(3S,4R)-(4-Methyl-pyrrolidin-3-yl)-(2-phenyl-quinazolin-4-yl)-amine

A. (3S,4S)-1-Benzyl-4-methyl-pyrrolidine-3-carboxylic acid methyl ester

Trifluoroacetic acid (0.16 ml, 2.00 mmol) is added to a stirred solution of benzyl-methoxymethyl-trimethylsilanylmethyl-amine (7.11 g, 29.96 mmol, Terao, Y.*et al, Chem. Pharm. Bull.*; 1985; 33(7); 2762-2766.) and methyl crotonate (2.0g, 19.98 mmol) in methylene chloride (40 ml) at 0°C for 2 h. Saturated sodium carbonate is added and the reaction extracted with methylene chloride. The combined layers are dried with sodium sulfate and concentrated. The residue is purified by silica gel chromatography using ether:methylene chloride (1:9) as eluant, followed by another purification by silica gel chromatography using ether:methylene chloride (gradient of 1:49 to 5:95) as eluant to give (3S, 4S)-1-Benzyl-4-methyl-pyrrolidine-3-carboxylic acid methyl ester (3.79 g):
H NMR ($CDCl_3$) δ 7.32-7.24 (m, 5H), 3.68 (s, 3H), 3.67-3.54 (m, 2H), 2.87-2.75 (m, 3H), 2.57-2.49 (m, 2H), 2.24-2.19 (dd, 1H, J = 9.0, 6.6 Hz), 1.14-1.12 (d, 3H, J = 6.6 Hz);

FAB MS *m/z* found 234 (MH^+).

B. (3S,4R)-1-Benzyl-3-[(1,1-dimethyl-ethyl)-oxy-carbonyl-amino]-4-methyl-pyrrolidine

Potassium hydroxide (0.91 g, 16.24 mmol) is added to a stirred solution of (3S, 4S)-1-Benzyl-4-methyl-pyrrolidine-3-carboxylic acid methyl ester (3.79 g, 16.24 mmol), prepared as in Part A, in ethanol (95% solution, 160 ml) and the solution heated to reflux for 16 h. The solution is cooled to 0°C, hydrochloric acid (4N in 1,4-dioxane, 4.0 ml, 16.24 mmol) added, and the solution stirred for 30 mins. The potassium chloride salts are filtered out and the resulting solution concentrated. The residue is taken up in *tert*-butanol (162 ml) and triethyl amine (1.81 g, 17.86 mmol) added. Diphenyl phosphoryl azide (4.9 ml, 17.86 mmol) is then added, and the solution heated to reflux for 16 h. The solution is concentrated, saturated sodium carbonate added, and the reaction extracted with ethyl acetate. The combined layers are dried with sodium sulfate and concentrated. Methanol:ethyl acetate (1:3) is added and a white solid precipitated out of solution to give (3S, 4R)-1-Benzyl-3-[(1,1-dimethyl-ethyl)-oxy-carbonyl-amino]-4-methyl-pyrrolidine (0.59 g):
^1H NMR ($CDCl_3$)δ 7.33-7.23 (m, 5H), 4.88-4.86 (m, 1H), 3.69 (m, 1H), 3.56 (s, 2H), 3.02-2.98 (m, 1H), 2.63-2.61 (m, 2H), 1.98-1.89 (m, 2H), 1.43 (s, 9H), 1.10-1.08 (d, 3H, J = 6.7 Hz);
FAB MS *m/z* found 291 (MH^+).

C. (3S,4R)-(1-Benzyl-4-methyl-pyrrolidin-3-yl)-(2-phenyl-quinazolin-4-yl)-amine

(3S, 4R)-1-Benzyl-3-[(1,1-dimethyl-ethyl)-oxy-carbonyl-amino]-4-methyl-pyrrolidine (0.59 g, 2.03 mmol), prepared as in Part B, taken up in a solution of trifluoroacetic acid:anisole:water (8:1:1, 20 ml) at room temperature and stirred for 16 h. The solution is concentrated, the residue is then taken up in tetrahydrofuran (20 ml) and triethylamine (1.2 ml, 8.12 mmol) added. 4-Chloro-2-phenyl quinazoline (0.49 g, 2.03 mmol) is added and the solution heated to reflux for 16 h. Saturated sodium carbonate is added and the reaction extracted with ethyl acetate. The combined layers are dried with sodium sulfate and concentrated. The residue is purified by silica gel chromatography using hexane:ethyl acetate (1:1) as eluant to

give (3S, 4R)-(1-Benzyl-4-methyl-pyrrolidin-3-yl)-(2-phenyl-quinazolin-4-yl)-amine (0.59 g):
^{1}H NMR ($CDCl_3$) δ 8.58-8.55 (dd, 2H, *J* = 7.8, 1.9 Hz), 7.91-7.88 (d, 1H, *J* = 8.3 Hz), 7.71-7.65 (m, 2H), 7.52-7.44 (m, 3H), 7.39-7.23 (m, 6H), 6.25-6.23 (d, 1H, *J* = 7.8 Hz), 4.67-4.65 (m, 1H), 3.64-3.53 (m, 2H), 3.18-3.13 (m, 1H), 2.89-2.82 (m, 2H), 2.25-2.24(m, 1H), 2.01-1.95 (m, 1H), 1.27-1.20 (m, 3H);
FAB MS *m/z* found 395 (MH^+).

D. (3S,4R)-(4-Methyl-pyrrolidin-3-yl)-(2-phenyl-quinazolin-4-yl)-amine

Ammonium formate (0.47 g, 7.48 mmol) is added to a solution of (3S, 4R)-(1-Benzyl-4-methyl-pyrrolidin-3-yl)-(2-phenyl-quinazolin-4-yl)-amine (0.59 g, 1.50 mmol), prepared as in Part C, in methanol (30 ml) under argon. Then, 5% palladium on carbon (0.15 g, 25 wt%) is added and the solution is heated at reflux for 16 h. The solution is purged with nitrogen, filtered through Celite®, and concentrated to give the title compound (0.46 g) which is used directly without further purification:
^{1}H NMR (CD_3OD) δ 8.45-8.42 (m, 2H), 8.34-8.31 (d, 1H, *J* = 8.0Hz), 7.86-7.81 (m, 2H), 7.57-7.49 (m, 4H), 4.00-3.96 (m, 1H), 3.73-3.72 (m, 1H), 3.41-3.37 (m, 1H), 3.15-3.08 (dd, 1H, *J* = 11.5, 9.3 Hz), 2.81-2.70 (m, 1H), 1.31-1.29 (d, 3H, *J* = 6.9 Hz);
FAB MS *m/z* found 305 (MH^+).

Intermediate 27

2-Benzyl-4-(2-bromoethyl)phenol

A. 3-Bromo-4-methoxyphenethyl alcohol

4-Methoxyphenethyl alcohol (50.0 g, 329 mmole) is dissolved in methylene chloride (300 mL) and cooled to 0°C. Bromine (20.0 mL, 388 mmole) is added slowly over 35 minutes. The mixture is stirred at 0°C for 60 minutes , then at 23°C for 90 minutes. The solution is recooled to 0°C and saturated aqueous sodium bisulfite is added until the red color disappeared. The mixture is concentrated to the

aqueous layer. Ethyl acetate (300 mL) is added and the mixture is washed with water (2 x 100 mL), dried ($MgSO_4$) and concentrated in vacuo to provide 3-bromo-4-methoxyphenethyl alcohol (85.33 g) as a yellow liquid.
^1H NMR ($CDCl_3$) δ 7.40 (s, 1H), 7.12 (m, 1H), 6.84 (m, 1H), 3.86 (s, 3H), 3.81 (t, 2H), 2.79 (t, 2H) ppm.

B. 2-[2-(3-Bromo-4-methoxyphenyl)ethyl]tetrahydropyran

3-Bromo-4-methoxyphenethyl alcohol (85.33 g, 369 mmole), prepared as in Part A, is dissolved in methylene chloride (400 mL) and cooled to 0°C. Pyridinium p-toluenesulfonate (0.74 g, 2.94 mmole) is added. Dihydropyran (41 mL, 449 mmole) is added dropwise over 10 minutes. The mixture is stirred at 0°C for 2 hours, then at 23°C for 18 hours. Water (200 mL) is added and the biphasic solution is concentrated to the aqueous layer. The mixture is extracted with diethyl ether (5 x 100 mL). The combined organics are dried ($MgSO_4$) and concentrated in vacuo to afford 2-[2-(3-bromo-4-methoxyphenyl)ethyl]tetrahydropyran as a dark liquid (100.13 g).
^1H NMR ($CDCl_3$) δ 7.41 (m, 1H), 7.13 (m, 1H), 6.90 (m, 1H), 4.48 (m, 1H), 3.84 (s, 3H), 3.48 (m, 2H), 3.44 (t, 2H), 2.80 (t, 2H), 1.84-1.43 (m, 6H) ppm.

C. {2-Methoxy-5-[2-(tetrahydropyran-2-yloxy)ethyl]phenyl}phenyl methanol

2-[2-(3-Bromo-4-methoxyphenyl)ethyl]tetrahydropyran (10.32 g, 32.8 mmole), prepared as in Part B, is dissolved in tetrahydrofuran (50 mL) and cooled to -78°C. The reaction vessel is evacuated and refilled with nitrogen. Butyllithium (40 mL of a 1.6M solution in hexanes, 64 mmole) is added dropwise over 20 minutes and the solution is stirred at -78°C for 60 minutes. Benzaldehyde (3.70 mL, 36.4 mmole) is dissolved in tetrahydrofuran (10 mL) and slowly added. The solution is stirred at -78°C for 90 minutes, then warmed slowly to 23°C and stirred for 18 hours. Water (150 mL) is added and the two layers are separated. The aqueous layer is extracted with ethyl acetate (3 x 25 mL). The combined organics are dried ($MgSO_4$) and concentrated in vacuo. The residue is chromatographed on silica gel and eluted with

70:30 hexanes:ethyl acetate to afford {2-methoxy-5-[2-(tetrahydropyran-2-yloxy)ethyl]phenyl}phenyl methanol as a yellow oil (5.51 g).
^{1}H NMR ($CDCl_3$) δ 7.39-7.24 (m, 5H), 7.21 (m, 1H), 7.16 (d, 1H), 6.89 (d, 1H), 6.00 (m, 1H), 4.57 (br s, 1H), 3.85 (m, 1H), 3.77 (s, 3H), 3.75 (m, 1H), 3.56 (m, 1H), 3.41 (m, 1H), 2.81 (t, 2H), 1.81-1.43 (m, 6H) ppm.

D. Acetic acid {2-methoxy-5-[2-tetrahydropyran-2-yloxy)ethyl]phenyl}phenyl methyl ester

{2-Methoxy-5-[2-(tetrahydropyran-2-yloxy)ethyl]phenyl}phenyl methanol (5.51 g, 16.1 mmole), prepared as in Part C, is dissolved in methylene chloride (35 mL) and cooled to 0°C. Pyridine (2.50 mL, 30.9 mmole) and 4-DMAP (0.21 g, 1.71 mmole) are added. Acetic anhydride (1.70 mL, 18.0 mmole) is added and the mixture is warmed to 23°C and stirred for 90 minutes. Water (100 mL) is added and the two layers are separated. The aqueous layer is extracted with methylene chloride (2 x 25 mL). The combined organics are dried ($MgSO_4$) and concentrated in vacuo. The residue is purified by silica gel chromatography and eluted with 70:30 hexanes:ethyl acetate to provide acetic acid {2-methoxy-5-[2-tetrahydropyran-2-yloxy)ethyl]phenyl}phenyl methyl ester as a yellow oil (4.69 g).
^{1}H NMR ($CDCl_3$) δ 7.36-7.19 (m, 7H), 7.11 (d, 1H), 6.87 (d, 1H), 4.58 (m, 1H), 3.90 (m, 1H), 3.77 (s, 3H), 3.75 (m, 1H), 3.57 (m, 1H), 3.41 (m, 1H), 2.82 (t, 2H), 2.14 (s, 3H), 1.81-1.42 (m, 6H) ppm.

E. 2-[2-(3-Benzyl-4-methoxyphenyl)ethoxy]tetrahydropyran

A clean dry 3 neck 250 mL flask is charged with 20% $Pd(OH)_2$ on carbon (0.88 g, 1.25 mmole) and placed under nitrogen. Acetic acid {2-methoxy-5-[2-tetrahydropyran-2-yloxy)ethyl]phenyl}phenyl methyl ester (4.69 g, 12.2 mmole), prepared as in Part D, is dissolved in methanol (35 mL) and is slowly added. The atmosphere is changed to hydrogen (balloon pressure) and the mixture is vigorously stirred for 4 hours. The mixture is filtered through a pad of Celite and the filter cake is washed with methylene chloride (4 x 10 mL). The combined filtrates are concentrated in vacuo. The residue is chromatographed on silica gel and eluted with

80:20 hexanes:ethyl acetate to yield 2-[2-(3-benzyl-4-methoxyphenyl)ethoxy]tetrahydropyran as a clear colorless oil (3.16 g).
^{1}H NMR ($CDCl_3$) δ 7.25-7.12 (m, 5H), 7.04 (d, 1H), 6.97 (s, 1H), 6.89 (d, 1H), 4.57 (m, 1H), 3.95 (s, 2H), 3.84 (q, 1H), 3.78 (s, 3H), 3.75 (m, 1H), 3.56 (q, 1H), 3.41 (m, 1H), 2.79 (t, 2H), 1.81-1.44 (m, 6H) ppm.

F. 2-(3-Benzyl-4-methoxyphenyl)ethanol

2-[2-(3-Benzyl-4-methoxyphenyl)ethoxy]tetrahydropyran (3.16 g, 9.70 mmole), prepared as in Part E, is dissolved in methanol (20 mL). p-Toluenesulfonic acid (0.18 g, 0.94 mmole) is added and the mixture is stirred at 23°C for 60 minutes. Triethylamine (0.26 mL) is added and the mixture is concentrated to provide 2-(3-benzyl-4-methoxyphenyl)ethanol as a clear colorless oil (2.93 g) that is used without further purification.
^{1}H NMR ($CDCl_3$) δ 7.24-7.15 (m, 5H), 7.04 (d, 1H), 6.91 (s, 1H), 6.80 (d, 1H), 3.92 (s, 2H), 3.79 (s, 3H), 3.77 (t, 2H), 2.77 (t, 2H) ppm.

G.2-Benzyl-4-(2-bromoethyl)anisole

2-(3-Benzyl-4-methoxyphenyl)ethanol (2.93 g, 12.1 mmole), prepared as in Part F, is dissolved in methylene chloride (30 mL) and cooled to 0°C. Triphenylphosphine (3.24 g, 12.4 mmole) is added, followed by slow addition of bromine (0.62 mL, 12.0 mmole). The mixture is warmed to 23°C and stirred for 3 hours. The solution is concentrated in vacuo and the residue is chromatographed on silica gel and eluted with 80:20 hexanes:ethyl acetate to afford 2-benzyl-4-(2-bromoethyl)anisole as a yellow liquid (2.83 g).
^{1}H NMR ($CDCl_3$) δ 7.26-7.17 (m, 5H), 7.01 (d, 1H), 6.89 (s, 1H), 6.80 (d, 1H), 3.93 (s, 2H), 3.79 (s, 3H), 3.46 (t, 2H), 3.03 (t, 2H) ppm.

H. 2-Benzyl-4-(2-bromoethyl)phenol

2-Benzyl-4-(2-bromoethyl)anisole (0.75 g, 2.47 mmole), prepared as in Part G, is added to a 50 mL flask. Boron tribromide (3.00 mL of a 1.0 M solution in

methylene chloride , 3.0 mmole) is added and the solution turned dark brown. The mixture is allowed to stir at 23°C for 2 hours. The solution is cooled to -78°C and methanol (~1-2 mL) is added. The solution is concentrated in vacuo. The residue is dissolved in toluene (5 mL) and concentrated in vacuo to yield the title compound as a dark brown oil (0.72 g) that is used without further purification.
^{1}H NMR ($CDCl_3$) d 7.27-7.20 (m, 5H), 6.98 (m, 2H), 6.75 (d, 1H), 3.98 (s, 2H), 3.50 (t, 2H), 3.05 (t, 2H) ppm.

Intermediate 28

3-(N-Acetyl)amino-4-methoxyphenethyl p-toluenesulfonate

A. 4-Methoxyphenethyl acetate

4-Methoxyphenethyl alcohol (10.24 g, 67.3 mmole) is dissolved in methylene chloride (150 mL) and cooled to 0°C. Pyridine (8.00 mL, 98.9 mmole) is added, followed by 4-DMAP (0.78 g, 6.41 mmole) and acetic anhydride (7.50 mL, 79.5 mmole). The solution is warmed to 23°C and stirred for 2 hours. Water (200 mL) is added and the two layers are separated. The aqueous layer is extracted with methylene chloride (2 x 25 mL). The combined organics are dried ($MgSO_4$) and concentrated in vacuo to afford 4-methoxyphenethyl acetate as a yellow liquid (14.32 g) that is used without further purification.
^{1}H NMR ($CDCl_3$) δ 7.13 (d, 2H), 6.81 (d, 2H), 4.22 (t, 2H), 3.79 (s, 3H), 2.84 (t, 2H), 2.02 (s, 3H) ppm.

B. 3-Nitro-4-methoxyphenethyl acetate

4-Methoxyphenethyl acetate (14.32 g, 73.8 mmole), prepared as in Part A, is dissolved in acetic acid (100 mL). The solution is cooled to 0°C and concentrated nitric acid (14.5 mL, 232 mmole) is added, followed by sodium nitrite (7.62 g, 110 mmole). The solution is stirred at 0°C for 2 hours, then at 23°C for 3 hours. The suspension is recooled to 0°C and concentrated nitric acid (14 mL) is added. The mixture is stirred at 0°C for 30 minutes, then is warmed to 23°C and stirred for 18

hours. Water (300 mL) is added and the mixture is extracted with ethyl ether (7 x 50 mL). The combined organics are washed with water (4 x 100 mL), dried ($MgSO_4$) and concentrated in vacuo to provide 3-nitro-4-methoxyphenethyl acetate (21.78 g) as an orange oil contaminated with acetic acid. The mixture is carried on without further purification.
^1H NMR ($CDCl_3$) d 7.70 (s, 1H), 7.39 (d, 1H), 7.01 (d, 1H), 4.24 (t, 2H), 3.92 (s, 3H), 2.91 (t, 2H), 2.02 (s, 3H) ppm.

C. 3-Amino-4-methoxyphenethyl acetate

To a clean dry flask is placed 10% palladium on carbon (5.02 g, 4.71 mmole). 3-Nitro-4-methoxyphenethyl acetate (21.78 g, 91.1 mmole), prepared as in Part B, is dissolved in isopropanol/ethyl acetate (75 mL/75 mL) and slowly added. The atmosphere is changed to hydrogen and the reaction vessel is pressurized to 50 psi and shaken for 4 hours (hydrogen uptake is very rapid). The mixture is filtered through a pad of Celite. The filter cake is washed with methylene chloride (3 x 20 mL). The combined filtrates are concentrated in vacuo to afford 3-amino-4-methoxyphenethyl acetate (14.98 g) as a dark red oil. The material is stored in the refrigerator and used without further purification. ^1H NMR ($CDCl_3$) δ 6.69 (d, 1H), 6.58 (m, 2H), 4.21 (t, 2H), 3.82 (s, 3H), 2.79 (t, 2H), 2.03 (s, 3H) ppm.

D. 3-(N-Acetyl)amino-4-methoxyphenethyl acetate

3-Amino-4-methoxyphenethyl acetate (1.06 g, 5.07 mmole), prepared as in Part C, is dissolved in methylene chloride (15 mL) and cooled to 0°C. Pyridine (2.00 mL, 24.7 mmole) and 4-DMAP (0.0654 g, 0.54 mmole) are added. Acetyl chloride (0.400 mL, 5.63 mmole) is added and the solution is stirred at 0°C for 45 minutes. Water (20 mL) is added and the two layers are separated. The aqueous layer is extracted with methylene chloride (2 x 5 mL). The combined organics are dried ($MgSO_4$) and concentrated in vacuo. The residue is chromatographed on silica gel and eluted with a) 60:40 ethyl acetate:hexanes; b) 70:30 ethyl acetate:hexanes to afford 3-(N-acetyl)amino-4-methoxyphenethyl acetate (0.48 g) as a yellow solid.

^{1}H NMR ($CDCl_3$) d 8.24 (s, 1H), 7.73 (br s, 1H), 6.83 (d, 1H), 6.79 (d, 1H), 4.22 (t, 2H), 3.82 (s, 3H), 2.86 (t, 2H), 2.19 (s, 3H), 2.01 (s, 3H) ppm.

E. 3-(N-Acetyl)amino-4-methoxyphenethyl alcohol

3-(N-Acetyl)amino-4-methoxyphenethyl acetate (0.48 g, 1.93 mmole), prepared as in Part D, is dissolved in 4/1/1 tetrahydrofuran/methanol/water (12 mL) and cooled to 0°C. Lithium hydroxide (0.21 g, 4.93 mmole) is added and the mixture is stirred at 0°C for 90 minutes. Saturated aqueous ammonium chloride (20 mL) is added and the mixture is extracted with ethyl acetate (2 x 10 mL). The combined organics are dried ($MgSO_4$) and concentrated in vacuo to provide 3-(N-acetyl)amino-4-methoxyphenethyl alcohol (0.34 g) as a light yellow solid that is used without further purification. ^{1}H NMR ($CDCl_3$) δ 8.25 (s, 1H), 7.76 (br s, 1H), 6.88 (d, 1H), 6.79 (d, 1H), 3.84 (s, 3H), 3.82 (t, 2H), 2.81 (t, 2H), 2.19 (s, 3H) ppm.

F. 3-(N-Acetyl)amino-4-methoxyphenethyl p-toluenesulfonate

3-(N-Acetyl)amino-4-methoxyphenethyl alcohol (0.34 g, 1.63 mmole), prepared as in Part E, is dissolved in pyridine (7 mL) and cooled to 0°C. p-Toluene sulfonyl chloride (0.32 g, 1.68 mmole) is added. The solution immediately turned red and then faded back into yellow. The mixture is stirred at 0°C and slowly warmed to 23°C over 4 hours. Water (50 mL) is added and the mixture is extracted with ethyl acetate (4 x 10 mL). The combined organics are dried ($MgSO_4$) and concentrated in vacuo. The residue is chromatographed on silica gel and eluted with 70:30 ethyl acetate:hexanes to yield the title compound (0.26 g) as a white solid. ^{1}H NMR ($CDCl_3$) δ 8.11 (s, 1H), 7.69 (m, 3H), 7.24 (d, 2H), 6.81 (d, 1H), 6.77 (d, 1H), 4.18 (t, 2H), 3.82 (s, 3H), 2.85 (t, 2H), 2.42 (s, 3H), 2.18 (s, 3H) ppm.

Intermediate 29

Toluene-4-sulfonic acid 2-(3-acetyl-4-methoxyphenyl)ethyl ester

A. 1-{2-Methoxy-5-[2-(tetrahydropyran-2-yloxy)ethyl]phenyl}ethanol

2-Methoxy-5-[2-(tetrahydropyran-2-yloxy)ethyl]benzaldehyde (4.03 g, 15.3 mmole), prepared as in Intermediate 38B, is dissolved in tetrahydrofuran (20 mL) and is cooled to -78°C. Methyllithium (30.0 mL of a 1.4M solution, 42 mmole) is added and the mixture is allowed to warm to 23°C over 60 minutes. The solution is stirred at 23°C for 90 minutes before water (50 mL) is slowly added (gas evolution!). The two layers are separated and the aqueous layer is extracted with ethyl acetate (2 x 10 mL). The combined organics are dried ($MgSO_4$) and concentrated in vacuo. The residue is chromatographed on silica gel and eluted with 60:40 hexanes:ethyl acetate to afford 1-{2-methoxy-5-[2-(tetrahydropyran-2-yloxy)ethyl]phenyl}ethanol as a yellow oil (1.54 g).

^1H NMR ($CDCl_3$) δ 7.20 (s, 1H), 7.11 (m, 1H), 6.80 (d, 1H), 5.08 (m, 1H), 4.59 (br s, 1H), 3.92 (m, 1H), 3.84 (s, 3H), 3.79 (m, 1H), 3.58 (m, 1H), 3.44 (m, 1H), 2.85 (t, 2H), 1.84-1.44 (m, 6H), 1.43 (d, 3H) ppm.

B. 1-{2-Methoxy-5-[2-(tetrahydropyran-2-yloxy)ethyl]phenyl}ethanone

1-{2-Methoxy-5-[2-(tetrahydropyran-2-yloxy)ethyl]phenyl}ethanol (1.07 g, 3.82 mmole), prepared as in Part A, is dissolved in N,N-dimethylformamide (10 mL). Pyridinium dichromate (1.84 g, 4.89 mmole) is added and the mixture is stirred at 23°C for 18 hours. Water (50 mL) is added and the mixture is extracted with diethyl ether (5 x 15 mL). The combined organics are washed with water (5 x 25 mL), then dried ($MgSO_4$) and concentrated in vacuo to afford 1-{2-methoxy-5-[2-(tetrahydropyran-2-yloxy)ethyl]phenyl}ethanone (0.98 g) as a dark orange liquid that is used without further purification.

^{1}H NMR ($CDCl_3$) δ 7.60 (s, 1H), 7.34 (d, 1H), 6.86 (d, 1H), 4.58 (br s, 1H), 3.88 (m, 1H), 3.85 (s, 3H), 3.77 (m, 1H), 3.57 (m, 1H), 3.44 (m, 1H), 2.83 (t, 2H), 2.59 (s, 3H), 1.81-1.43 (m, 6H) ppm.

C. 1-[5-(2-Hydroxyethyl)-2-methoxyphenyl]ethanone

1-[2-Methoxy-5-[2-(tetrahydropyran-2-yloxy)ethyl]phenyl}ethanone (0.98 g, 3.51 mmole), prepared as in Part B, is dissolved in methanol (10 mL). p-Toluenesulfonic acid (0.067 g, 0.35 mmole) is added and the solution turned bright yellow. The reaction is allowed to stir at 23°C for 2 hours. Triethylamine (0.08 mL) is added and the mixture is concentrated in vacuo to provide 1-[5-(2-hydroxyethyl)-2-methoxyphenyl]ethanone (0.80 g) as a green oil that is used without further purification.
^{1}H NMR ($CDCl_3$) d 7.60 (s, 1H), 7.33 (d, 1H), 6.91 (m, 1H), 3.87 (s, 3H), 3.82 (t, 2H), 2.80 (t, 2H), 2.59 (s, 3H) ppm.

D. Toluene-4-sulfonic acid 2-(3-acetyl-4-methoxyphenyl)ethyl ester

1-[5-(2-Hydroxyethyl)-2-methoxyphenyl]ethanone (0.80 g, 4.13 mmole) is dissolved in pyridine (4 mL). p-Toluenesulfonyl chloride (1.17 g, 6.14 mmole) is added and the solution is stirred at 23°C for 90 minutes. Water (25 mL) is added and the mixture is extracted with ethyl acetate (3 x 10 mL). The combined organics are dried ($MgSO_4$) and concentrated in vacuo. The residue is chromatographed on silica gel and eluted with 70:30 hexanes:ethyl acetate to afford the title compound (0.59 g,) as an orange oil.
^{1}H NMR ($CDCl_3$) δ 7.71 (d, 2H), 7.43 (s, 1H), 7.25 (m, 3H), 6.87 (d, 1H), 4.18 (t, 2H), 3.88 (s, 3H), 2.90 (t, 2H), 2.59 (s, 3H), 2.41 (s, 3H) ppm.

Intermediate 30

1-(6-Bromohexanoyl)-2-pyrrolidinone

2-Pyrrolidone (0.54 g, 6.31 mmole) is dissolved in tetrahydrofuran (10 mL) and cooled to -78°C. Butyllithium (4.3 mL of a 1.6 M solution in hexane, 6.9 mmole) is added and the mixture is stirred at -78°C for 40 minutes. 6-Bromohexanoyl chloride (1.00 mL, 6.53 mmole) is added and the solution is stirred at -78°C for 30 minutes. Saturated aqueous sodium chloride (50 mL) is added and the two layers are separated. The aqueous layer is extracted with ethyl acetate (2 x 10 mL). The combined organics are dried ($MgSO_4$) and concentrated in vacuo to provide the title compound (1.86 g) as a dark yellow liquid that is used without further purification. ^1H NMR ($CDCl_3$) δ 3.80 (t, 2H), 3.40 (t, 2H), 2.92 (t, 2H), 2.60 (t, 2H), 2.04 (m, 2H), 1.91 (m, 2H), 1.65 (m, 2H), 1.49 (m, 2H) ppm.

Intermediate 31

1-(2-Chloroethyl)-3-methylsulfonyl-2-imidazolidinone

A. 1-(2-Chloroethyl)-2-imidazolidinone

1-(2-Hydroxyethyl)-2-imidazolidinone (18.94 g, 146 mmole) is dissolved in chloroform (200 mL). Thionyl chloride (12.7 mL, 174 mmole) is added and the solution is heated to reflux for 90 minutes. The solution is concentrated in vacuo. The residue is extracted with ethyl acetate (3 x 50 mL) and the combined organics are filtered and concentrated in vacuo to afford 1-(2-chloroethyl)-2-imidazolidinone as an orange solid that is used directly without further purification. ^1H NMR ($CDCl_3$) δ 9.18 (br s, 1H), 3.72-3.55 (m, 8H) ppm.

B. 1-(2-Chloroethyl)-3-methylsulfonyl-2-imidazolidinone

1-(2-Chloroethyl)-2-imidazolidinone (1.49 g, 10.0 mmole), prepared as in Part A, is dissolved in tetrahydrofuran (15 mL) and cooled to -78°C. Butyllithium (7.00 mL of a 1.6 M solution in hexanes, 11.2 mmole) is added and the solution is stirred at -78°C for 30 minutes. Methanesulfonyl chloride (0.82 mL, 10.6 mmole) is added and the solution is stirred at -78°C for 30 minutes. Brine (50 mL) is added and the two layers are separated. The aqueous layer is extracted with ethyl acetate (2 x 10 mL).

The combined organics are dried ($MgSO_4$) and concentrated in vacuo to provide the title compound (2.23 g) as a dark brown solid.
^1H NMR ($CDCl_3$) δ 3.88 (t, 2H), 3.69-3.58 (m, 6H), 3.29 (s, 3H) ppm.

Intermediate 32

1-(2-Chloroethyl)-3-trimethylacetyl-2-imidazolidinone

1-(2-Chloroethyl)-2-imidazolidinone (1.38 g, 9.31 mmole) is dissolved in tetrahydrofuran (15 mL) and is cooled to -78°C. Butyllithium (6.50 mL of a 1.6 M solution in hexanes, 10.4 mmole) is added and the solution is stirred at -78°C for 30 minutes. Trimethylacetyl chloride (1.20 mL, 9.74 mmole) is added and the solution is stirred at -78°C for 30 minutes. Brine (50 mL) is added and the two layers are separated. The aqueous layer is extracted with ethyl acetate (2 x 10 mL). The combined organics are dried ($MgSO_4$) and concentrated in vacuo to afford the title compound (1.90 g) as a dark yellow oil that is used without further purification.
^1H NMR ($CDCl_3$) δ 3.85 (t, 2H), 3.68 (m, 2H), 3.59 (m, 4H), 1.38 (s, 9H) ppm.
Analytical Calculated: C,68.3%; H, 7.1%; N, 17.1%; Found: C, 68.07%; H, 7.11%; N, 16.74%.

Intermediate 33

1-(4-Bromobutyryl)-δ-valerolactam

δ-Valerolactam (1.45 g, 14.7 mmole) is dissolved in tetrahydrofuran (20 mL) and is cooled to -78°C. Butyllithium (10.0 mL of a 1.6 M solution in hexanes, 16.0 mmole) is added and the solution is stirred at -78°C for 60 minutes. 4-Bromobutyryl chloride (1.80 mL, 15.5 mmole) is added and the solution is allowed to slowly warm to 23°C over 2 hours, then stir at 23°C for 60 minutes. Water (50 mL) is added and the two layers are separated. The aqueous layer is extracted with ethyl acetate (2 x 10 mL). The combined organics are dried ($MgSO_4$) and concentrated in vacuo. The residue is chromatographed on silica gel and eluted with 1/1 ethyl acetate/hexanes to afford the title compound (3.43 g) as a light yellow oil.

^{1}H NMR ($CDCl_3$) δ 3.69 (m, 2H), 3.45 (t, 2H), 3.04 (t, 2H), 2.59 (m, 2H), 2.21 (m, 2H), 1.83 (m, 4H) ppm.

Intermediate 34

5-[2-((3-(R)-(N-Phenylmethyl-(2-phenyl-quinazolin-4-yl)aminomethyl))-pyrrolidin-1-yl)-ethyl]-2-methoxy-benzenesulfonamide bistrifluoroacetate

A. N-(Phenylmethyl)-5-oxo-1-(1-(R)-phenylethyl)-3-(R)-pyrrolidinecarboxamide

A mixture of 5-Oxo-1-(1-(R)-phenylethyl)-3-(R)-pyrrolidinecarboxylic acid, methyl ester (9g; 36.39 mmol)(Culbertson, T.P., *et al, J. Med. Chem., 30,* 1711 (1987)) and benzylamine (30g) is allowed to stand at 23°C for 48h. The excess benzylamine is removed by evaporation and the residue triturated with EtOAc:hexane (1:2; 50 mL). The resulting white solid is collected by filtration to afford N-(Phenylmethyl)-5-oxo-1-(1-(R)-phenylethyl)-3-(R)-pyrrolidinecarboxamide (7.33g). A portion is crystallized from EtOAc-hexane.

^{1}H NMR ($CDCl_3$) δ 7.35-7.20 (m, 10H), 6.02 (br s, 1H), 5.43 (q, J = 7.2 Hz, 1H), 4.40 (d, J = 5.6 Hz, 2H), 3.57 (dd, J = 7.6 Hz, J' = 9.6 Hz, 1H), 3.11 (t, J = 8.8 Hz, 1H), 2.87 (quin, J = 8.4 Hz, 1H), 2.64 (ABX system, J_{ab} = 16.4 Hz, J_{ax} = 8.8 Hz, J_{bx} = 9.6 Hz, 2H), 1.50 (d, J = 7.2 Hz, 3H).
Anal. Found: C, 74.35; H, 6.99; N, 8.65. $C_{20}H_{22}N_2O_2$ Requires: C, 74.51; H, 6.88; N, 8.69%.

B. 3-(S)-(Phenylmethylaminomethyl)-1-(1-(R)-phenylethyl)pyrrolidine

A solution of N-(phenylmethyl)-5-oxo-1-(1-(R)-phenylethyl)-3-(R)-pyrrolidinecarboxamide (6.5 g; 20.96 mmol), prepared as in Part A, in THF (100 mL) is added to a suspension of $LiAlH_4$ (2 g) in THF (100 mL) and the mixture heated under reflux for 2 h. The mixture is cooled to 0 °C and carefully treated with water until all excess reagent is decomposed. The resulting mixture is filtered through celite and the solvent evaporated. The residue is diluted with water (100 mL) and

extracted with EtOAc (4 x 50 mL). The combined organic layers are dried (K_2CO_3) and evaporated to afford 3-(S)-(Phenylmethylaminomethyl)-1-(1-(R)-phenylethyl)pyrrolidine as an oil (5.93 g).
^1H NMR ($CDCl_3$) δ 7.35-7.19 (m, 10H), 3.78 (s, 2H), 3.17 (q, J = 6.4 Hz, 1H), 2.85 (t, 8.4 Hz, 1H), 2.59 (d, J = 7.2 Hz, 2H), 2.55-2.27 (m, 3H), 2.11 (dd, J = 6.4 Hz, J' = 9.2 Hz, 1H), 1.95 (m, 1H), 1.45 (m, 1H), 1.38 (d, J = 6.8 Hz, 3H).
^{13}C NMR ($CDCl_3$) δ 145.59, 140.45, 128.29, 128.19, 127.97, 127.06, 126.78, 126.72, 65.84, 57.71, 54.51, 54.00, 52.58, 37.47, 28.89, 23.17.

C. 3-(R)-[N-Phenylmethyl-(2-Phenyl-quinazolin-4-yl)aminomethyl]-1-(1-(R)-phenylethyl)pyrrolidine

A solution of 3-(S)-(Phenylmethylaminomethyl)-1-(1-(R)-phenylethyl)pyrrolidine (700 mg; 2.48 mmol), prepared as in Part B, 4-chloro-2-phenyl-quinazoline (1.2 g; 5.0 mmol) and triethylamine (4 mL) in ethanol (5 mL) is heated at 140 °C in a sealed tube for 4 h. The solvent is evaporated and the residue is partitioned between EtOAc (30 mL) and water (20 mL). The organic layer is separated, dried (MgSO4) and evaporated. The residue is purified by chromatography using 25% EtOAc-hexane as eluent to afford 3-(R)-[N-Phenylmethyl-(2-Phenyl-quinazolin-4-yl)aminomethyl]-1-(1-(R)-phenylethyl)pyrrolidine as a yellow foam (1.166 g).
^1H NMR ($CDCl_3$) δ 8.58 (m, 2H), 7.97 (m, 2H), 7.70 (m , 1H), 7.55-7.23 (m, 14H), 5.04 (AB system, J_{ab} = 16.2 Hz, 2H), 3.80 (ABX system, J_{ab} = 13.5 Hz, J_{ax} = 6.9 Hz, J_{bx} = 7.8 Hz, 2H), 3.16 (q, J = 6.3 Hz, 1H), 2.88 (m, 1H), 2.66 (m, 2H), 1.98 (m, 1H), 1.53 (m, 1H), 1.33 (d, J = 6.6 Hz, 3H).

D. 3-(R)-[N-Phenylmethyl-(2-Phenyl-quinazolin-4-yl)aminomethyl]pyrrolidine

A mixture of ammonium formate (600 mg), 10% Pd/C (500 mg) and 3-(R)-[N-phenylmethyl-(2-Phenyl-quinazolin-4-yl)aminomethyl]-1-(1-(R)-phenylethyl)pyrrolidine (1.16 g), prepared as in Part C, in methanol (45 mL) and water (15 mL) is heated under reflux for 2h. The mixture is cooled and additional ammonium formate (600 mg) is added followed by a further 2h at reflux. The cooled

mixture is filtered through celite and the solvent evaporated. The residue is partitioned between water (30 mL) and EtOAc (50 mL) and the organic layer is separated, dried ($MgSO_4$) and evaporated to afford 3-(R)-[N-Phenylmethyl-(2-Phenyl-quinazolin-4-yl)aminomethyl]pyrrolidine as a brown foam (630 mg).
^1H NMR (CD_3OD) δ 8.42 (m, 2H), 8.07 (m, 1H), 7.78 (m, 1H), 5.12 (s, 2H), 3.95 (m, 2H), 3.50-2.90 (m, 6H), 2.20 (m, 1H), 1.80 (m, 1H).
HPLC and mass spectral analysis shows the presence of 25% of debenzylated material.

E. 5-[2-((3-(R)-(N-Phenylmethyl-(2-phenyl-quinazolin-4-yl)aminomethyl))-pyrrolidin-1-yl)-ethyl]-2-methoxy-benzenesulfonamide bistrifluoroacetate

A mixture of 3-(R)-[N-phenylmethyl-(2-Phenyl-quinazolin-4-yl)aminomethyl]pyrrolidine (600 mg; 1.521 mmol), prepared as in Part D, 5-(2-chloroethyl)-2-methoxy-benzenesulfonamide (725 mg; 3.05 mmol), potassium carbonate (850 mg), and sodium iodide (915 mg) in 95% EtOH (6 mL) is heated at 140 °C in a sealed tube for 6h. The solvent is evaporated and the residue treated with water (20 mL) and extracted with EtOAc (2 x 20 mL). The combined organic layers are dried (MgSO4) and evaporated. Purification by chromatography using 50% EtOAc-hexane then EtOAc the MeOH as eluent afforded a light brown foam (630 mg). A portion of this material (300 mg) is purified by reverse phase HPLC to afford the title compound as a yellow powder (130 mg).
^1H NMR (DMSO-d_6) δ 10.00 (br d , 1H), 8.41 (d, J = 6 Hz, 2H), 8.10-7.80 (m, 3H), 7.60-7.20 (m, 12H), 7.13 (d, J = 8.4 Hz, 1H), 7.02 (m, 2H), 5.20 (br s, 2H), 3.85 (s, 3H), 4.10-2.70 (m, 12H), 2.30-1.60 (m, 2H).
Anal. Found: C, 52.75; H, 4.63; N, 7.71. $C_{35}H_{37}N_5O_3S.2.5CF_3CO_2H.H_2O$
Requires: C, 52.75; H, 4.59; N, 7.69%.

Intermediate 35

5-[2-((3-(S)-(N-Phenylmethyl-(2-phenyl-quinazolin-4-yl)aminomethyl))-pyrrolidin-1-yl)-ethyl]-2-methoxy-benzenesulfonamide bistrifluoroacetate

A. N-(Phenylmethyl)-5-oxo-1-(1-(R)-phenylethyl)-3-(S)-pyrrolidinecarboxamide

Synthesized in a manner similar to Intermediate 34A, using 5-oxo-1-(1-(R)-phenylethyl)-3-(S)-pyrrolidinecarboxylic acid, methyl ester (97%)(Culbertson, T.P., *et al, J. Med. Chem., 30,* 1711 (1987)). A portion is crystallized from EtOAc-hexane to yield N-(Phenylmethyl)-5-oxo-1-(1-(R)-phenylethyl)-3-(S)-pyrrolidinecarboxamide .
^{1}H NMR ($CDCl_3$) d 7.40-7.10 (m, 10H), 6.13 (m, 1H), 5.45 (q, J = 7.2 Hz, 1H), 4.34 (d, J = 5.7 Hz, 2H), 3.47 (dd, J = 9.0 Hz, J' = 9.9 Hz, 1H), 3.22 (dd, J = 6.9 Hz, J' = 9.6 Hz, 1H), 3.01 (quin, J = 6.6 Hz, 1H), 2.64 (ABX system, J_{ab} = 16.8 Hz, J_{ax} = 8.1 Hz, J_{bx} = 9.3 Hz, 2H), 1.51 (d, J = 7.2 Hz, 3H).
Anal. Found: C, 74.53; H, 6.91; N, 8.70. $C_{20}H_{22}N_2O_2$ Requires: C, 74.51; H, 6.88; N, 8.69%.

B. 3-(R)-(Phenylmethylaminomethyl)-1-(1-(R)-phenylethyl)pyrrolidine

Prepared in as in Intermediate 34 B from N-(phenylmethyl)-5-oxo-1-(1-(R)-phenylethyl)-3-(S)-pyrrolidinecarboxamide (100%), prepared as in Part A, to yield 3-(R)-(Phenylmethylaminomethyl)-1-(1-(R)-phenylethyl)pyrrolidine.
[^{1}H NMR ($CDCl_3$) δ 7.35-7.20 (m, 10H), 3.76(s, 2H), 3.16 (q, J = 6.4 Hz, 1H), 2.75 (m, 1H), 2.65 (dd, J = 8.0 Hz, J' = 8.8 Hz, 1H), 2.58 (d, J = 7.2 Hz, 2H), 2.31 (m, 2H), 2.1 (dd, J = 7.2 Hz, J' = 9.2 Hz, 1H), 2.00 (m, 1H), 1.44 (m, 2H), 1.37 (d, J = 6.4 Hz, 3H).
^{13}C NMR ($CDCl_3$) δ 145.55, 140.43, 128.30, 128.20, 127.99, 127.11, 126.79, 126.76. 65.86, 57.85, 54.36, 54.05, 52.43, 37.68, 28.87, 23.10.

C. 3-(S)-[N-Phenylmethyl-(2-Phenyl-quinazolin-4-yl)aminomethyl]-1-(1-(R)-phenylethyl)pyrrolidine

Prepared as in Intermediate 34 C from 3-(R)-(Phenylmethylaminomethyl)-1-(1-(R)-phenylethyl)pyrrolidine (91%), prepared as in Part B to yield 3-(S)-[N-Phenylmethyl-(2-Phenyl-quinazolin-4-yl)aminomethyl]-1-(1-(R)-phenylethyl)pyrrolidine .

^{1}H NMR ($CDCl_3$) δ 8.52 (m, 2H), 7.98 (dd, J = 8.4 Hz, J' = 12.4 Hz, 2H), 7.69 (t, J = 7.6 Hz, 1H), 7.53-7.15 (m, 14H), 5.04 (s, 2H), 3.79 (d, 7.2 Hz, 2H), 3.12 (q, 6.4 Hz, 1H), 2.85 (m, 1H), 2.54 (m, 2H), 2.39 (m, 2H), 1.98 (m, 1H), 1.46 (m, 1H), 1.28 (d, J = 6.4 Hz, 3H).

^{13}C NMR ($CDCl_3$) δ 164.10, 159.09, 153.14, 145.41, 138.73, 137.72, 132.10, 129.96, 129.11, 128.99, 128.72, 128.36, 128.22, 127.34, 127.04, 126.79, 124.87, 124.5, 115.22, 65.49, 56.90, 55.17, 54.92, 52.28, 35.88, 28.65.

D. 3-(S)-[N-Phenylmethyl-(2-Phenyl-quinazolin-4-yl)aminomethyl]pyrrolidine

Prepared as in Intermediate 34 D from 3-(S)-[N-phenylmethyl-(2-Phenyl-quinazolin-4-yl)aminomethyl]-1-(1-(R)-phenylethyl)pyrrolidine, prepared as in Part C, to yield 3-(S)-[N-Phenylmethyl-(2-Phenyl-quinazolin-4-yl)aminomethyl]pyrrolidine.

E. 5-[2-((3-(S)-(N-Phenylmethyl-(2-phenyl-quinazolin-4-yl)aminomethyl))-pyrrolidin-1-yl)-ethyl]-2-methoxy-benzenesulfonamide bistrifluoroacetate

Prepared as in Intermediate 34 E from 3-(S)-[N-phenylmethyl-(2-Phenyl-quinazolin-4-yl)aminomethyl]pyrrolidine, prepared as in Part D to yield the title compound.

$[\alpha]_D$ -3.03° (c=0.89; MeOH).

Anal. Found: C, 51.28; H, 4.28; N, 7.44. $C_{35}H_{37}N_5O_3S.3CF_3CO_2H.0.5H_2O$ Requires: C, 521.36; H, 4.31; N, 7.30%.

Intermediate 36

3-(3-Indolyl)-1-propylmethanesulfonate

A. 3-(3-Indolyl)-1-propanol

A slurry of lithium aluminum hydride (1.5 g, 40 mmol) in tetrahydrofuran (50 mL) is stirred at 25°C as 3-indole-3-propionic acid (5.00 g, 26.43 mmol) is added in small portions. The mixture is heated under reflux for 6 h and is stirred at 25°C for 14 h. The mixture is then chilled to 0°C and is treated sequentially with 1.5 mL of water, 1.5 mL of 15% aqueous sodium hydroxide, and 4.5 mL of water. The mixture is filtered and the filtrate is concentrated in vacuo to provide 3-(3-indolyl)-1-propanol (4.38 g) as an oil.
^{1}H NMR ($CDCl_3$) δ 8.00 (bs, 1H, NH), 7.62 (d, J = 8 Hz, 1H, ArH), 7.39 (d, J = 8 Hz, 1H, ArH), 7.22 (t, 1H, J = 8 Hz, ArH), 7.17 (t, J = 8 Hz, 1H, ArH), 7.01 (s, 1H, ArH), 3.78 (t, J = 6 Hz, 2H, CH_2O), 2.83 (t, J = 6 Hz, 2H, $ArCH_2$), 2.03 (m, 2H, CH_2) ppm.

B. 3-(3-Indolyl)-1-propylmethanesulfonate

A solution of 3-(3-indolyl)-1-propanol (2.20 g, 12.56 mmol), prepared as in Part A, in pyridine (12 mL) is chilled to 0°C and treated with methanesulfonyl chloride (1.45 mL, 18.7 mmol). After 1 h at 0°C and 3 h at 25°C the mixture is chilled to 0°C and treated with water. The mixture is extracted with ethyl acetate. The combined organic phases are washed with water and saturated aqueous sodium bisulfate. Drying over magnesium sulfate and concentration in vacuo provided the title compound (2.26 g) as an oil.
^{1}H NMR ($CDCl_3$) δ 8.02 (bs, 1H, NH), 7.60 (d, J = 8 Hz, 1H, ArH), 7.39 (d, J = 8 Hz, 1H, ArH), 7.24 (t, J = 8 Hz, 1H, ArH), 7.15 (t, J = 8 Hz, 1H, ArH), 7.02 (s, 1H, ArH), 4.27 (t, J = 7 Hz, 2H, CH_2O), 2.99 (s, 3H, CH_3S), 2.94 (t, 2H, J = 6 Hz, CH_2Ar), 2.18 (m, 2H, CH_2) ppm.

Intermediate 37

2-(3-Hydroxymethyl-4-methoxyphenyl)ethylmethanesulfonate

A. 2(3-Bromo-4-methoxyphenyl)ethanol

A solution of 4-methoxyphenethyl alcohol (50.0 g, 329 mmol) in 300 mL of dichloromethane is chilled to 0°C and is treated with bromine (20 mL, 387 mmol) dropwise. After 1 h at 0°C and 2 h at 25°C the mixture is chilled to 0°C and is treated carefully with saturated aqueous sodium bisulfite until the bromine is consumed. The mixture is concentrated in vacuo and the residue is taken up in ethyl acetate. The mixture is washed with water, brine, and is dried over magnesium sulfate. Concentration in vacuo afforded 2(3-bromo-4-methoxyphenyl)ethanol (75.4 g) as an oil.
^{1}H NMR ($CDCl_3$) δ 7.41 (s, 1H, ArH), 7.13 (d, J = 8 Hz, 1H, ArH), 6.82 (d, J = 8 Hz, 1H, ArH), 3.87 (s, 1H, CH_3O), 3.82 (t, J = 7 Hz, 2H, CH_2O), 2.78 (t, J = 7 Hz, 2H, $ArCH_2$), 2.18 (s, 1H, OH) ppm.

B. 2(3-Bromo-4-methoxyphenyl)ethyl (1,1,2-Trimethyl)propyldimethylsilylether

A solution of 2(3-bromo-4-methoxyphenyl)ethanol (75.4 g, 326 mmol), prepared as in Part A, in N,N-dimethylformamide (300 mL) is treated with imidazole (45.0 g, 660 mmol) and (1,1,2-trimethyl)propyldimethylsilyl chloride (68 mL, 346 mmol). The mixture is stirred at 25°C for 14 h, then is diluted with water and extracted with ethyl acetate. The combined organics are washed with water, brine, and are dried over magnesium sulfate. Concentration in vacuo afforded 2(3-bromo-4-methoxyphenyl)ethyl (1,1,2-trimethyl)propyldimethylsilyl ether (110 g) as an oil.
^{1}H NMR ($CDCl_3$) δ 7.41 (s, 1H, ArH), 7.12 (d, J = 8 Hz, 1H, ArH), 6.81 (d, J = 8 Hz, 1H, ArH), 3.88 (s, 1H, CH_3O), 3.73 (t, J = 7 Hz, 2H, CH_2O), 2.73 (t, J = 7 Hz, 2H, $ArCH_2$) 1.60 (m, 1H, CH), 0.88 (d, J = 6 Hz, 6H, CH_3), 0.81 (s, 6H, CH_3), 0.02 (s, 6H, CH_3) ppm.

C. 2(3-Formyl-4-methoxyphenyl)ethyl (1,1,2-Trimethyl)propyldimethylsilyl ether

A solution of 2(3-bromo-4-methoxyphenyl)ethyl (1,1,2-trimethyl)propyldimethylsilylether (1.74 g, 4.66 mmol), prepared as in Part B, in tetrahydrofuran (5 mL) is chilled to -78°C under nitrogen as 6.10 mL (0.46 mmol) of n-butyllithium (6.1 mL, 1.55 M in hexane, 9.46 mmol) is added. After 30 min at -78°C N,N-dimethylformamide (1 mL, excess) is added and the mixture is warmed to 25°C. Water is added and the mixture is extracted with ethyl acetate. The combined organics are washed with water, brine, and are dried over magnesium sulfate. Concentration in vacuo afforded 2(3-formyl-4-methoxyphenyl)ethyl (1,1,2-trimethylpropyl)dimethylsilyl ether (1.45 g) as an oil.
^{1}H NMR ($CDCl_3$) δ 10.60 (s, 1H, CHO), 7.80 (s, 1H, ArH), 7.58 (d, J = 8 Hz, 1H, ArH), 7.03 (d, J = 8 Hz, 1H, ArH), 4.04 (s, 1H, CH_3O), 3.84 (t, J = 7 Hz, 2H, CH_2O), 2.90 (t, J = 7 Hz, 2H, $ArCH_2$), 1.60 (m, 1H, CH), 0.89 (d, J = 6 Hz, 6H, CH_3), 0.84 (s, 6H, CH_3), 0.05 (s, 6H, CH_3) ppm.

D. 2-(3-Formyl-4-methoxyphenyl)ethanol

2-(3-Formyl-4-methoxyphenyl)ethyl(1,1,2-trimethyl)propyldimethylsilylether (1.50 g, 4.58 mmol) in tetrahydrofuran (10 mL) is treated at 25°C with tetrabutylammonium fluoride (6 mL, 1 M in tetrahydrofuran, 6 mmol). After 2 h at 25°C the mixture is treated with water and is extracted with ethyl acetate. The organic phases are washed with saturated aqueous ammonium chloride and brine. The mixture is dried over magnesium sulfate and concentrated in vacuo to afford 2(3-formyl-4-methoxyphenyl)ethanol (1.49 g crude) as an oil.
^{1}H NMR ($CDCl_3$) δ 10.41 (s, 1H, CHO), 7.69 (s, 1H, ArH), 7.43 (d, J = 8 Hz, 1H, ArH), 6.93 (d, J = 8 Hz, 1H, ArH), 3.91 (s, 1H, CH_3O), 3.81 (t, J = 6.5 Hz, 2H, CH_2O), 2.81 (t, J = 6.5 Hz, 2H, $ArCH_2$) ppm.

E. 2-(3-Hydroxymethyl-4-methoxyphenyl)ethylmethanesulfonate

2-(3-Formyl-4-methoxyphenyl)ethanol (1.40 g), prepared as in Part D, is stirred in pyridine (3 mL) at 0°C as methanesulfonyl chloride (0.7 mL, 9.0 mmol) is

added. After 2 h at 0°C the mixture is treated with 10 mL of water and 10 mL of isopropanol. Sodium borohydride (1.0 g, excess) is added and the mixture is stirred at 0°C for 1 h and at 25°C for 0.5 h. Water is added and the mixture is extracted with ethyl acetate. The combined organics are washed with water, saturated aqueous sodium bisulfate, and brine. Drying over magnesium sulfate and concentration in vacuo afforded the title compound (2.0 g) as an oil.
^{1}H NMR ($CDCl_3$) δ 7.50 (s, 1H, ArH), 7.11 (d, J = 8 Hz, 1H, ArH), 6.82 (d, J = 8 Hz, 1H, ArH), 4.63 (s, 2H, $ArCH_2O$), 4.38 (t, J = 7 Hz, 2H, CH_2O), 3.85 (s, 1H, CH_3O), 2.98 (t, J = 7 Hz, 2H, $ArCH_2$), 2.84 (s, 3H, CH_3S) ppm.

Intermediate 38

2(3-Methanesulfonylaminomethyl-4-methoxyphenyl)ethyl p-toulenesulfonate

A. 2-(3-Bromo-4-methoxyphenyl)ethyl-2-Tetrahydropyranylether

A mixture of 2-(3-bromo-4-methoxyphenyl)ethanol (132 g, 571 mmol) in 500 mL of dichloromethane at 0°C is treated with dihydropyran (65 mL, 711 mmol) and pyridinium p-toulenesulfonate (1.0 g). After 2 h at 0°C and 48 h at 25°C the mixture is concentrated in vacuo and the residue is slurried in water. The mixture is extracted with ethyl acetate. The organic phases are dried over magnesium sulfate and are concentrated in vacuo to provide 2-(3-bromo-4-methoxyphenyl)ethyl-2-tetrahydropyranylether (169 g) as an oil.
^{1}H NMR ($CDCl_3$) δ 7.43 (s, 1H, ArH), 7.14 (d, J = 8 Hz, 1H, ArH), 6.80 (d, J = 8 Hz, 1H, ArH), 4.58 (s, 1H, CHO), 3.90 (m, 1H, CH_2O), 3.86 (s, 3H, CH_3O), 3.73 (m, 1H, CH_2O), 3.56 (m, 1H, CHO), 3.42 (m, 1H, CHO), 2.80 (t, J = 7 Hz, 2H, CH_2Ar), 1.81 (m, 1H, CH_2), 1.68 (m, 1H, CH_2), 1.57 (m, 4H, CH_2) ppm.

B. 2-(3-Formyl-4-methoxyphenyl)ethyl-2-Tetrahydropyranylether

A solution of 2-(3-bromo-4-methoxyphenyl)ethyl-2-tetrahydropyranylether (40.0 g, 127 mmol), prepared as in Part A, in 250 mL of tetrahydrofuran is chilled to -78°C under nitrogen as n-butyllithium (170 mL, 1.55 M in hexanes, 262 mmol) is

added. The mixture is stirred for 30 min at -78°C . N,N-Dimethylformamide (25 mL, excess) is added and the mixture is warmed to 25°C over 1 h. Saturated ammonium chloride is added and the mixture is diluted with water and is extracted with ethyl acetate. The combined organics are washed with water, brine, and are dried over magnesium sulfate. Concentration in vacuo afforded 2-(3-formyl-4-methoxyphenyl)ethyl-2-tetrahydropyranylether (32.8 g) as an oil.
^{1}H NMR ($CDCl_3$) δ 10.51 (s, 1H, CHO), 7.65 (s, 1H, ArH), 7.43 (d, J = 8 Hz, 1H, ArH), 6.85 (d, J = 8 Hz, 1H, ArH), 4.57 (s, 1H, CHO), 4.03 (s, 3H, CH_3O), 3.94 (m, 1H, CH_2O), 3.73 (m, 1H, CH_2O), 3.60 (m, 1H, CHO), 3.43 (m, 1H, CHO), 2.90 (t, J = 7 Hz, 2H, CH_2Ar), 1.81 (m, 1H, CH_2), 1.67 (m, 1H, CH_2), 1.56 (m, 4H, CH_2) ppm.

C. 2-(3-Methanesulfonylaminomethyl-4-methoxyphenyl)ethanol

A solution of 2-(3-formyl-4-methoxyphenyl)ethyl-2-tetrahydropyranylether (1.30 g, 4.92 mmol), prepared as in Part B, in dichloromethane (20 mL) is treated with triethylamine (3.5 mL, 25.1 mmol) and methanesulfonamide (470 mg, 4.94 mmol). The mixture is chilled to 0°C and titanium tetrachloride (0.82 mL, 7.48 mmol) is added dropwise. After 30 min at 0°C the mixture is quenched with methanol and the resulting mixture is added to a mixture of sodium borohydride (2 g, excess) in 100 mL of isopropanol at 0°C. After 2 h at 25°C the mixture is treated with saturated aqueous sodium carbonate and then is diluted with water. The mixture is extracted with ethyl acetate and the organics are dried over magnesium sulfate and are concentrated in vacuo.

The crude product is treated in methanol (30 mL) with p-toluenesulfonic acid (0.5 g). After 1 h at 25°C the mixture is quenched with triethylamine (1 mL). Concentration in vacuo and chromatography on 60 g of silica gel (elution with 30% ethyl acetate:hexane followed by 70% ethyl acetate:hexane followed by ethyl acetate) afforded 2-(3-methanesulfonylaminomethyl-4-methoxyphenyl)ethanol (486 mg) as an oil.
^{1}H NMR ($CDCl_3$) δ 7.18 (d, J = 8 Hz, 1H, ArH), 7.13 (s, 1H, ArH), 6.82 (d, J = 8 Hz, 1H, ArH), 4.93 (bt, J = 6 Hz, 1H, NH), 4.28 (d, J = 6 Hz, 2H, CH_2N), 8.82 (s, 3H, CH_3O), 3.80 (t, J = 7 Hz, 2H, CH_2O), 2.80 (t, J = 7 Hz, 2H, $ArCH_2$), 2.79 (s, 3H, CH_3S) ppm.

D. 2(3-Methanesulfonylaminomethyl-4-methoxyphenyl)ethyl-p-toulenesulfonate

A solution of 2-(3-methanesulfonylaminomethyl-4-methoxyphenyl)ethanol (360 mg, 1.39 mmol), prepared as in Part C, in 3 mL of pyridine is treated with 0.5 g of 4-dimethylaminopyridine and p-toluenesulfonyl chloride (400 mg, 2.09 mmol). The mixture is kept at 25°C for 24 h, then is quenched with water and extracted with ethyl acetate. The organics are washed with water, saturated aqueous sodium bisulfate, and brine. Drying over magnesium sulfate and concentration in vacuo afforded the title compound (390 mg) as an oil.
^{1}H NMR ($CDCl_3$) δ 7.71 (d, J = 8 Hz, 2H, ArH), 7.29 (d, J = 8 Hz, 1H, ArH), 7.09 (d, J = 8 Hz, 1H, ArH), 7.00 (s, 1H, ArH), 6.79 (d, J = 8 Hz, 1H, ArH), 4.90 (bt, J = 6 Hz, 1H, NH), 4.21 (d, J = 6 Hz, 2H, CH_2N), 4.08 (t, J = 6 Hz, 2H, CH_2O), 3.81 (s, 3H, CH_3O), 2.87 (t, J = 6 Hz, 2H, $ArCH_2$), 2.72 (s, 3H, CH_3S) ppm.

Intermediate 39

2-[3-(1-Succinimidoylmethyl)-4-methoxyphenyl]ethyl p-Toluenesulfonate

A. 2-(3-Hydroxymethyl-4-methoxyphenyl)ethyl-2-Tetrahydropyranyl Ether

A solution of 2-(3-formyl-4-methoxyphenyl)ethyl-2-tetrahydropyranylether (30.0 g, 114 mmol), prepared as in Intermediate 38B, in methanol (250 mL) is chilled to 0°C as sodium borohydride (5.00 g, 131 mmol) is added in small portions. After 2 h at 0°C the mixture is quenched with saturated aqueous sodium carbonate. The mixture is extracted with ethyl acetate. The combined organics are dried over magnesium sulfate and concentrated in vacuo to provide 2-(3-hydroxymethyl-4-methoxyphenyl)ethyl-2-tetrahydropyranylether (26.8 g) as an oil.
^{1}H NMR ($CDCl_3$) δ 7.12 (bs, 2H, ArH), 6.81 (d, J = 8 Hz, 1H, ArH), 4.65 (s, 2H, CH_2O), 4.58 (s, 1H, CHO), 3.83 (s, 3H, CH_3O), 3.78 (t, 2H, J = 7 Hz, CH_2O), 3.56 (m, 1H, CHO), 3.42 (m, 1H, CHO), 2.81 (t, J = 7 Hz, 2H, CH_2Ar), 1.79 (m, 1H, CH_2), 1.66 (m, 1H, CH_2), 1.58 (m, 4H, CH_2) ppm.

B. 2-[3-(1-Succinimidoylmethyl)-4-methoxyphenyl]ethyl-2-Tetrahydropyranylether

A solution of 2-(3-hydroxymethyl-4-methoxyphenyl)ethyl-2-tetrahydropyranylether (3.00 g, 11.27 mmol), prepared as in Part A, in tetrahydrofuran (50 mL) is chilled to 0°C and treated with triphenylphosphine (3.25 g, 12.40 mmol) and succinimide (1.25 g,12.3 mmol), followed by diethyl azodicarboxylate (2.15 mL, 12.33 mmol). After 30 min at 0°C and 1 h at 25°C the mixture is partially concentrated in vacuo and purified by chromatography on 150 g of silica gel (elution with 30% ethyl acetate:hexane followed by 50% ethyl acetate:hexane followed by 70% ethyl acetate - hexane followed by ethyl acetate) to afford 2-[3-(1-succinimidoylmethyl)-4-methoxyphenyl]ethyl-2-tetrahydropyranylether (2.334 g) as an oil.
^{1}H NMR ($CDCl_3$) δ 7.08 (d, J = 8 Hz, 1H, ArH), 6.93 (s, 1H, ArH), 6.77 (d, J = 8 Hz, 1H, ArH), 4.69 (s, 2H, CH_2N), 4.55 (bs, 1H, CHO), 3.85 (m, 1H, CH_2O), 3.80 (s, 3H, CH_3O), 3.76 (m, 1H, CH_2O), 3.532 (m, 1H, CH_2O), 3.42 (m, 1H, CH_2O), 2.80 (t, J = 7 Hz, 2H, CH_2Ar), 2.73 (s, 4H, CH_2CO), 1.80 (m, 1H, CH_2), 1.64 (m, 1H, CH_2), 1.52 (m, 2H, CH_2) ppm.

C. 2-[3-(1-Succinimidoylmethyl)-4-methoxyphenyl]ethyl-p-toluenesulfonate

A solution of 2-[3-(1-succinimidoylmethyl)-4-methoxyphenyl]ethyl 2-tetrahydropyranylether (1.40 g, 4.03 mmol), prepared as in Part B, in 50 mL of methanol is treated with p-toluenesulfonic acid (0.25 g) and is kept at 25°C for 2 h. The mixture is treated with 1 mL of triethylamine and is concentrated in vacuo. Chromatography of the residue through silica gel (elution with 40% ethyl acetate followed by 80% ethyl acetate - hexane) afforded the alcohol, which is stirred in pyridine (5 mL) at 25°C as 4-dimethylaminopyridine (50 mg) and p-toluenesulfonyl chloride (1.2 g, 6.29 mmol) are added. After 12 h at 25°C the mixture is quenched with water and extracted with ethyl acetate. The organics are washed with water, saturated aqueous sodium bisulfate, and are dried over magnesium sulfate. Concentration under reduced pressure afforded the title compound (1.25 g) as an oil.
^{1}H NMR ($CDCl_3$) δ 7.80 (d, J = 8 Hz, 2H, ArH), 7.39 (d, J = 8 Hz, 2H, ArH), 7.08 (d, J = 8 Hz, 1H, ArH), 6.98 (s, 1H, ArH), 6.82 (d, J = 8 Hz, 1H, ArH), 4.79 (s, 2H,

CH_2N), 4.22 (t, J = 7 Hz, 2H, CH_2O), 3.90 (s, 3H, CH_3O), 2.97 (t, J = 7 Hz, 2H, $ArCH_2$), 2.87 (s, 4H, CH_2CO), 2.52 (s, 3H, CH_3Ar) ppm.

Intermediate 40

2-(3-Bromo-4-methoxyphenyl)ethylmethanesulfonate

A solution of 2-(3-bromo-4-methoxyphenyl)ethanol (3.00 g, 12.98 mmol), prepared as in Intermediate 37A, in pyridine (5 mL) is stirred at 0°C as methanesulfonyl chloride (1.5 mL, 19.4 mmol) is added. After 1 h at 0°C and 2 h at 25°C the mixture is treated with water and is diluted with ethyl acetate. The organic phase is washed with water, saturated aqueous sodium bisulfate, and brine. Drying over magnesium sulfate and concentration in vacuo afforded the title compound (3,86 g) as an oil. ^1H NMR ($CDCl_3$) δ 7.41 (s, 1H, ArH), 7.16 (d, J = 8 Hz, 1H, ArH), 6.82 (d, J = 8 Hz, 1H, ArH), 3.38 (t, J = 7 Hz, 1H, CH_2O), 3.84 (s, 3H, CH_3O), 3.98 (t, J = 7 Hz, 1H, $ArCH_2$), 3.88 (s, 3H, CH_3S) ppm.

Intermediate 41

2-[3-(2-Tetrahydrofuryl)-4-methoxyphenyl]ethyl-p-toluenesulfonate

A. 2-[3-(2-Hydroxy-2-tetrahydrofuryl)-4-methoxyphenyl]ethyl (1,1,2-Trimethyl)propyldimethylsilylether

A solution of 2-(3-bromo-4-methoxyphenyl)ethyl (1,1,2-trimethyl)propyldimethylsilyl ether (5.74 g, 15.4 mmol), prepared as in Intermediate 37B, in tetrahydrofuran (50 mL) is chilled to -78°C and is treated under nitrogen with n-butyllithium (10.9 mL, 1.55 M in hexanes, 16.9 mmol). After 30 min at -78°C the mixture is treated dropwise with γ- butyrolactone (1.73 g, 20.10 mmol). After warming to 25°C over 4 h the mixture is treated with saturated aqueous ammonium chloride. The mixture is diluted with water and is extracted with ethyl acetate. The organics are washed thoroughly with water, brine, are dried over magnesium sulfate, and concentrated in vacuo to provide 2-[3-(2-hydroxy-2-tetrahydrofuryl)-4-

methoxyphenyl]ethyl (1,1,2-trimethyl)propyldimethylsilylether (6.09 g crude) as an oil.
^{1}H NMR ($CDCl_3$) δ 7.58 (s, 1H, ArH), 7.35 (dd, J = 8, 2 Hz, 1H, ArH), 6.90 (d, J = 8 Hz, 1H, ArH), 3.92 (s, 3H, CH_3O), 3.78 (m, 4H, CH_2O), 2.80 (t, J = 7 Hz, 2H, $ArCH_2$), 2.52 (m, 2H, CH_2), 2.00 (m, 2H, CH_2), 1.60 (m, 1H, CH), 1.60 (m, 1H, CH), 0.85 (d, J = 7 Hz, 6H, CH_3), 0.82 (s, 6H, CH_3), 0.04 (s, 6H, CH_3) ppm.

B. 2-[3-(2-Tetrahydrofuryl)-4-methoxyphenyl]ethyl (1,1,2-Trimethylpropyl)dimethylsilylether

A solution of 2-[3-(2-hydroxy-2-tetrahydrofuryl)-4-methoxyphenyl]ethyl (1,1,2-trimethyl)propyldimethylsilyl ether (4.00 g, 10.51 mmol), prepared as in Part A, in dichloromethane (20 mL) is treated with triethylsilane (3.35 mL, 21.03 mmol). The mixture is chilled to 0°C as trifluoroacetic acid (1.7 mL, 22.1 mmol) is added. The mixture is kept at 0°C for 1 h and at 25°C for 6 h. The mixture is quenched with saturated aqueous sodium carbonate, is further diluted with water, and is extracted with ethyl acetate. The organic phases are washed with water, brine, and are dried over magnesium sulfate. Concentration in vacuo and chromatography of the residue on 60 g of silica gel (elution with 20% ethyl acetate:hexane followed by 40% ethyl acetate:hexane) afforded 2-[3-(2-tetrahydrofuryl)-4-methoxyphenyl]ethyl (1,1,2-trimethyl)propyldimethylsilylether (3.42 g) as an oil.
^{1}H NMR ($CDCl_3$) δ 7.25 (s, 1H, ArH), 7.07 (d, J = 8 Hz, 1H, ArH), 6.79 (d, J = 8 Hz, 1H, ArH), 5.15 (t, J = 7 Hz, 1H, CHO), 4.10 (dd, J = 8, 6.5 Hz, 1H, CH_2O), 3.90 (dd, J = 8, 6.5 Hz, 1H, CH_2O), 3.79 (s, 3H, CH_3O), 3.72 (t, J = 6 Hz, 2H, CH_2O), 2.78 (t, J = 6 Hz, 2H, $ArCH_2$), 2.38 (m, 1H, CH_2), 1.97 (m, 2H, CH_2), 1.68 (m, 1H, CH_2) 1.60 (m, 1H, CH), 0.83 (d, J = 7 Hz, 6H, CH_3), 0.81 (s, 6H, CH_3), 0.03 (s, 6H, CH_3) ppm.

C. 2-[3-(2-Tetrahydrofuryl)-4-methoxyphenyl]ethanol

A solution of 2-[3-(2-tetrahydrofuryl)-4-methoxyphenyl]ethyl (1,1,2-trimethyl)propyldimethylsilylether (1.82 g, 5.00 mmol), prepared as in Part B, in tetrahydrofuran (10 mL) is stirred at 25°C as tetrabutylammonium fluoride (7.00 mL,

1 M in tetrahydrofuran, 7.00 mmol) is added. After 2 h at 25°C the mixture is diluted with ethyl acetate and is washed with water, brine, and is dried over magnesium sulfate. Concentration in vacuo and chromatography on 80 g of silica gel (elution with 20% ethyl acetate:hexane followed by 50% ethyl acetate:hexane followed by ethyl acetate) afforded 2-[3-(2-tetrahydrofuryl)-4-methoxyphenyl]ethanol (1.05 g) as an oil.

^{1}H NMR ($CDCl_3$) δ 7.31 (s, 1H, ArH), 7.13 (dd, J = 8, 2 Hz, 1H, ArH), 6.81 (d, J = 8 Hz, 1H, ArH), 5.17 (t, J = 7 Hz, 1H, CHO), 4.17 (dd, J = 8, 7 Hz, 1H, CH_2O), 3.95 (dd, J = 8, 7 Hz, 1H, CH_2O), 3.84 (bs, 5H, CH_3O, CH_2O), 2.83 (t, J = 6 Hz, 2H, $ArCH_2$), 2.41 (m, 1H, CH_2), 2.00 (m, 2H, CH_2), 1.71 (m, 1H, CH_2) ppm.

D. 2-[3-(2-Tetrahydrofuryl)-4-methoxyphenyl]ethyl-p-toluenesulfonate

A solution of 2-[3-(2-tetrahydrofuryl)-4-methoxyphenyl]ethanol (1.05 g, 4.72 mmol), prepared as in Part C, in dichloromethane (25 mL) at 25°C is treated with triethylamine (1.7 mL, 12.1 mmol), 4-dimethylaminopyridine (100 mg), and p-toluenesulfonyl chloride (1.15 g, 6.03 mmol). After 10 h at 25°C the mixture is treated with water and is stirred at 25°C for 2 h. The mixture is extracted with ethyl acetate and the combined organics are washed with water, saturated aqueous sodium bisulfate, and brine. Drying over magnesium sulfate and concentration in vacuo afforded the title compound (1.28 g) as an oil. ^{1}H NMR ($CDCl_3$) δ 7.71 (d, J = 8 Hz, 2H, ArH), 7.29 (d, J = 8 Hz, 2H, ArH), 7.17 (s, 1H, ArH), 6.98 (dd , J = 8, 2 Hz, 1H, ArH), 6.71 (d, J = 8 Hz, 1H, ArH), 5.07 (t, J = 7 Hz, 1H, CHO), 4.16 (t, J = 7 Hz, 2H, CH_2O), 4.03 (dd, J = 8, 6.5 Hz, 1H, CH_2O), 3.88 (dd, J = 8, 6.5 Hz, 1H, CH_2O), 3.79 (s, 3H, CH_3O), 2.88 (t, J = 7 Hz, 2H, $ArCH_2$), 2.38 (m, 1H, CH_2), 1.93 (m, 2H, CH_2), 1.61 (m, 1H, CH_2) ppm.

Intermediate 42

2-(Methoxy-phenyl)-3H-quinazolin-4-one

A mixture of o-methoxybenzaldehyde (10g, 73.4 mmol), anthranilamide (10g, 73.4 mmol) and sodium bisulfite are dissolved in dimethylacetamide (85ml). The solution is heated to reflux for 2h. The solution is poured into water (1 liter) and filtered. The filter cake is washed with ethanol and ethyl ether. The product is dried under vacuum. The crude material is recrystallized from hot dimethylformamide to afford 14.94g of the title compound.

NMR ^{1}H (300MHz, DMSO) δ 12.08 (s, 1H), 8.15 (d, 8.8 Hz, 1H), 7.83 (t, 7.1Hz, 1H), 7.71 (m, 2H), 7.55 (m,2H), 7.18 (d, 8.3Hz, 1H), 7.1 (t, 7.6 Hz, 1H), 3.8 (s, 3H).

NMR ^{13}C (75MHz, DMSO) δ161.2, 157.1, 152.3, 149.0, 134.4, 132.2, 130.4, 127.4, 126.5, 125.8, 122.6, 120.9, 120.4, 111.8, 55.8.

Mas Spec; $[MH^{+}]$= 253.

C,H,N calcd for $C_{15}H_{12}O_2N_2$ C: 71.42, H: 4.79, N: 11.10.

Found C: 71.32, H: 4.83, N: 11.13.

Intermediate 43

2-(3-Trifluoromethyl-phenyl)-3H-quinazolin-4-one

A mixture of m-trifluromethylbenzaldehyde (5g, 28.7 mmol), anthranilamide (3.9g, 28.7 mmol) and sodium bisulfite are dissolved in dimethylacetamide (33ml). The solution is heated to reflux for 2h. The solution is poured into water (1 liter) and filtered. The filter cake is washed with ethanol and ethyl ether. The product is dried under vacuum. The crude material is recrystallized from hot dimethylformamide to afford 1.52g of title compound.

NMR ^{1}H (DMSO) δ 8.52 (s, 1H), 8.48 (d, 7.9Hz, 1H), 8.17 (dd, 0.44Hz, 6.9Hz, 1H), 7.95 (d, 8.2Hz, 1H), 7.85 (m, 3H), 7.56 (m, 1H).

NMR ^{13}C (75 MHz, DMSO) δ 162.21, 151.05, 148.51, 134.78, 133.75, 131.82, 129.91, 127.92, 127.88, 127.71, 127.07, 125.93, 124.55, 124.50, 121.22.

Mass Spec MH^+= 291
C,H,N calcd for $C_{15}H_9N_2O_1F_3$. C: 62.07, H: 3.13, N: 9.65.
Found. C: 62.02, H: 3.14, N: 9.64.

Intermediate 44

2-(4-Nitro-phenyl)-3H-quinazolin-4-one.

Synthesized in a manner similar to Intermediate 43, using p-nitrobenzaldehyde (11g, 73.4 mmol), to afford 4.47g of purified product .
^1H NMR (300MHz, DMSO) δ 8.43 (m, 4H), 8.18 (d, 7.6 Hz, 1H), 7.89 (t, 6.8 Hz, 1H), 7.79 (d, 7.8 Hz, 1H), 7.6 (t, 7.3 Hz, 1H).
^{13}C NMR (75 MHz, DMSO) δ 178.65, 150.97, 134.67, 133.89, 129.27, 129.09, 127.66, 127.21, 125.90, 123.66, 123.61, 114.53, 113.01, 110.18.

Intermediate 45

2-m-Tolyl-3H-quinazolin-4-one

Synthesized in a manner similar to Intermediate 43, using m-methylbenzaldehyde (10g, 83.3 mmol)to afford 5.06g of 2-m-Tolyl-3H-quinazolin-4-one.
^1H NMR (300 MHz, DMSO) δ 8.15 (dd, 1 Hz, 7.4 Hz, 1H), 8.01 (s, 1H), 7.96 (m, 1H), 7.8 (m, 1H), 7.33 (m, 1H), 7.48 (m, 2H), 7.45 (m, 1H).
Mass Spec MH^+= 236.98

Intermediate 46

2-Pyridinyl-4-yl-3H-quinazolin-4-one

Synthesized in a manner similar to Intermediate 43, using 4-pyridine carboxaldehyde (15g, 46.7 mmol)e to afford 3.5g of 2-Pyridinyl-4-yl-3H-quinazolin-4-one.

^{1}H NMR (300 MHz, DMSO) δ 12.73 (brs, 1H), 8.75 (s, 2H), 8.15-8.03 (m, 3H), 7.91-7.76 (m, 2H), 7.54 (m, 1H).
Mass Spec MH^+= 224.03

Intermediate 47

R-5-[2-(3-Amino-pyrrolidin-1-yl)-ethyl]-2-methoxy-benzenesulfonamide

A. (3R)-1-Benzyl-pyrrolidin-3-yl-t-butoxycarbonylamine

(3R)-(-)-1-Benzyl-3-aminopyrrolidine (20g, 113.5 mmol) is dissolved in acetonitrile. To this solution at 23°C is added di-t-butyl dicarbonate (29.7g, 136.2 mmol) and diisopropylethyl amine (23.7 mL, 136.2 mmol). The solution is stirred at 23°C for 4h. and concentrated in vacuo. The crude material is purified by flash chromatography (SiO_2, Ethyl acetate: Hexane 20: 80) to afford 25g of the title compound.
NMR ^{1}H (DMSO, 300MHz) δ 7.3 (s,5H), 6.95 (d,1H), 3.9 (brs,1H), 3.5 (s, 2H), 2.65 (t,1H), 2.4 (m, 2H), 2.2 (m, 1H), 2.0 (m, 1H), 1.55 (m, 1H), 1.3 (s, 9H).

B. (3R)-3-t-Butoxycarbonyl-aminopyrrolidine

10% palladium on carbon is added to a solution of (3R)-1-benzyl-pyrrolidin-3-yl-t-butoxycarbonylamine (25.0 g, 90.4 mmol), prepared as in Part A, in ethanol (180ml) under N_2. The flask is filled with an H_2 balloon then repeatedly evacuated and purged with hydrogen to remove all N_2, then stirred for 14 h. The solution is purged with N_2 filetered through Celite and concentrated to give (3R)-3-t-butoxycarbonyl-aminopyrrolidine (13.8g).
NMR ^{1}H ($CDCl_3$, 300MHz) δ 5.06 (d,1H, J=5.8Hz), 4.05 (s, 1H), 3.04 (br s, 1H), 3.02-2.96 (m, 2H), 2.86 (q, 1H, J=6.3 Hz), 2.74 (dd, 1H, J=11.2, 3.1 Hz), 2.07-2.00 (m, 1H), 1.57-1.51 (m, 1H), 1.38 (s, 9H).

C. (3R)-5-[2-(3-t-Butoxycarbonyl-amino-pyrrolidin-1-yl)-ethyl]-2-methoxy-benzenesulfonamide

(3R)-3-t-Butoxycarbonyl-aminopyrrolidine (13.82g, 89.7 mmol), prepared as in Part B, is taken up in 1,4 dioxane and treated successively with 5-(2-chloroethyl)-2-methoxy-benzenesulfonamide (17.25g, 89.7 mmol) diisopropylethyl amine (15.65 mL, 89.7 mmol), and sodium iodide (1.32g, 8.97 mmol). The mixture is refluxed overnite, cooled to ambient and filtered. The filtrate is diluted with ethyl acetate and washed with water. The combined organic extracts are dried (Na_2SO_4), filtered and concentrated. The crude material is purified by column chromatography (silica gel; methanol: methylene chloride 10:90) to afford 18g of 3(R)-5-[2-(3-t-Butoxycarbonyl-amino-pyrrolidin-1-yl)-ethyl]-2-methoxy-benzenesulfonamide.
NMR ^1H (DMSO, 300MHz) δ 7.55 (d, 1.9hz, 1H), 7.41 (dd, 2Hz, 8.3Hz, 1H), 7.1 (d, 8.3Hz, 1H), 7.07 (brs, 2H), 6.99 (d, 21Hz,1H), 3.84 (brs, 5H), 3.31 (brs, 1H), 2.81 (t, 8.8Hz, 1H), 2.71 (m, 2H), 2.57 (m, 2H), 2.27 (m, 1H), 1.98 (m, 1H), 1.56 (m, 1H), 1.35 (s, 9H).

D. R-5-[2-(3-Amino-pyrrolidin-1-yl)-ethyl]-2-methoxy-benzenesulfonamide

(3R)-5-[2-(3-t-Butoxycarbonyl-amino-pyrrolidin-1-yl)-ethyl]-2-methoxy-benzenesulfonamide (1g, 2.,5 mmol), prepared as in Part C, is taken up in dioxane/HCl (4N) and stirred at 23°C for 2h. and concentrated to afford the title compound as an oil.
NMR ^1H (DMSO, 300MHz) δ 8.8 (d, 2H), 7.7 (s, 1H), 7.5 (d, 1H), 7.2 (d, 2H), 7.0 (s, 2H), 3.9 (brs, 5H), 3.7-3.3 (m, 5H), 3.3-3.0 (m, 3H), 2.3-2.0 (m, 2H).

Intermediate 48

5-(2-chloroethyl)-2-methoxy-benzenesulfonamide

1-(2-chloroethyl)-4-methoxy benzene (56.5 g, 331 mmol) is cooled to 0 C and treated dropwise with chlorosulfonic acid (120 mL). The reaction is allowed to warm to 23 C and stirred for 4 h. The purple mixture is poured cautiously and slowly onto

ice. This mixture is extracted with EtOAc (2 x 750 mL) and the combined organic layers are dried ($MgSO_4$) and concentrated to a brown oil. The oil is dissolved in THF (310 mL), cooled to -20 C, and a large excess of ammonia is condensed into the flask. The reaction is stirred for 1h at -20 C, then allowed to warm to 23 C and stirred for 15h. The solvent is evaporated and the residue triturated with EtOAc. The off-white solid is washed with water and vacuum dried to afford the title compound as a white solid (36g).

^1H NMR (DMSO-d6) δ 7.62 (d, 1H, J = 2.2 Hz), 7.47 (dd, 1H, J = 8.6, 2.2 Hz), 7.14 (d, 1H, J = 8.5 Hz), 7.03 (s, 2H), 3.86 (s, 3H), 3.81 (t, 2H, J = 6.9 Hz), 3.00 (t, 2H, J = 6.8 Hz).

mp 158-161 C

Intermediate 49

2-phenyl-4-piperazin-1-yl-quinazoline

A suspension of 4-chloro-2-phenylquinazoline (AM-ex-OL, Aldrich) (20g, 83.1 mmol) and 1-benylpiperazine (14.4 mL, 83.1 mmol) in isoamyl alcohol (400 mL) is heated at 145 C for 3h. The solvent is evaporated and the residue taken up in CH_2Cl_2 (80 mL) and treated with HCl in Et_2O (250 mL of a 1N solution). The resulting suspension is stirred at 23 C for 1h, and the hydrochloride salt of the benzyl amine product collected by filtration (32g, 91%). A portion of this product (11.8g, 30.4 mmol) is taken up in MeOH (250 mL), cooled to -78 C, treated with 10% Pd/C (10g) and ammonium formate (9.59g, 152 mmol), and heated at reflux for 2h. The mixture is allowed to cool to 23 C, filtered through celite, and the solvent is evaporated. The residue is taken up in $CHCl_3$ (250 mL) and 2N NaOH (200 mL), and the organic layer is separated. The organic layer is washed with brine (1 x 200 mL), dried (K_2CO_3), and concentrated to afford the title compound as a yellow solid (3.3g).

^1H NMR ($CDCl_3$) δ 8.59 (m, 2H), 8.01 (d, 1H, J = 8.3 Hz), 7.93 (d, 1H, J = 8.3 Hz), 7.76 (dt, 1H, J = 7.1, 1.4 Hz), 7.51 (m, 4H), 3.88 (m, 4H), 3.17 (m, 4H).

C18H18N4 - 0.125 H2O requires C: 73.88, H: 6.29, N: 19.15, found C: 73.90, H: 6.22, N: 19.13.

mp 108-110 C

Intermediate 50

2-methoxy-5-(2-piperazin-1-yl-ethyl)-benzenesulfonamide dihydrochloride

A mixture of 5-(2-chloroethyl)-2-methoxy-benzenesulfonamide (41g, 188 mmol), prepared as in Intermediate 48, N-Boc piperazine (35g, 188 mmol), K_2CO_3 (78g, 564 mmol), and NaI (1g), in CH_3CN (800 mL) is stirred with a mechanical stirrer and heated at reflux for 18h. The mixture is filtered and concentrated to a yellow foam. The foam is purified by chromatography on silica using 5% MeOH: CH_2Cl_2 as eluent to afford the product as an oil. This oil is treated with 4N HCl in dioxane (400 mL) and stirred for 18h. The resulting precipitate is washed with Et_2O (3 x 200 mL) and dried to afford the title compound as a white solid (22g).
^1H NMR (DMSO-d6) d 9.86 (br, 2H), 7.66 (d, 1H, J = 1.9 Hz), 7.47 (dd, 1H, J = 8.5, 2.2 Hz), 7.17 (d, 1H, J = 8.5 Hz), 7.06 (s, 2H), 3.87 (s, 3H), 3.72 (m, 2H), 3.6 - 3.2 (m, 8H), 3.07 (m, 2H).
C13H23N3O3SCl2 - 0.5 H2O requires C: 40.95, H: 6.34, N: 11.02, found C: 40.50, H: 6.30, N: 10.89.

Intermediate 51

8-chloro-2-phenyl-3H-quinazolin-4-one

A. 2-nitro-3-chloro benzamide

A suspension of 3-chloro-2-nitro benzoic acid (10g, 49.6 mmol) in $SOCl_2$ (50 mL) is heated at reflux for 1 h. The solution is poured slowly into a mixture of concentrated NH_4OH (250 mL) and ice (200 mL). The precipitate is collected, washed with H_2O, and recrystallized from DMF to afford 2-nitro-3-chloro benzamide as an off-white solid (6.2 g).
^1H NMR (DMSO-d6) δ 8.34 (broad, 1H), 7.87 (m, 3H), 7.78 (dd, 1H, J = 7.8, 1.5 Hz), 7.70 (t, 1H, J = 8.1 Hz).

B. 2-amino-3-chloro benzamide

A suspension of 2-nitro-3-chloro benzamide (800 mg, 4 mmol), prepared as in Part A, in acetic acid (15 mL) is treated portionwise with zinc dust (1.05 g, 16 mmol) and stirred vigorously for 15h. The reaction mixture is diluted with CH_2Cl_2 (150 mL) and made basic with 2N NaOH. The organic layer is washed with H_2O (1 x 100 mL), brine (1 x 100 mL), dried (Na_2SO_4), and concentrated. The residue is purified by recrystallization from DMF to afford 2-amino-3-chloro benzamide as an off-white solid (100 mg).

^1H NMR (DMSO-d6) d 7.83 (broad, 1H), 7.47 (dd, 1H, J = 8.0, 1.4 Hz), 7.29 (dd, 1H, J = 7.8, 1.2 Hz), 7.24 (broad, 1H), 6.6 (broad, 2H), 6.47 (t, 1H, J = 7.8 Hz).

C. 8-chloro-2-phenyl-3H-quinazolin-4-one

A mixture of 2-amino-3-chloro benzamide (500 mg, 2.9 mmol), prepared as in Part B, benzaldehyde (295 mL, 2.9 mmol) and $NaHSO_3$ (483 mg, 4.64 mmol) in dimethylacetamide (10 mL) is heated at 150 C for 2h. The mixture is allowed to cool, and poured into H_2O (50 mL). The resulting solid is collected by filtration and recrystallized from DMF, to afford the title compound as a pale yellow solid (100 mg, 13%).

^1H NMR (DMSO-d6) δ 8.16 (m, 2H), 8.03 (d, 1H, J = 7.1 Hz), 7.91 (d, 1H, J = 7.6 Hz), 7.52 (m, 4H), 7.41 (t, 1H, J = 7.8 Hz)

FAB MS m/z found 257 (consistent for 1 chlorine) (MH+).

Intermediate 52

7-chloro-2-phenyl-3H-quinazolin-4-one

A. 2-nitro-4-chlorobenzamide

A suspension of 2-nitro 4-chlorobenzoic acid (10g, 49.6 mmol) in $SOCl_2$ (50 mL) is heated at reflux for 1 h. The solution is poured slowly into a mixture of concentrated NH_4OH (250 mL) and ice (200 mL). The precipitate is collected, washed with H_2O, and recrystallized from DMF to afford 2-nitro-4-chlorobenzamide as a tan solid (5.1 g).

^1H NMR (DMSO-d6) δ 8.19 (broad, 1H), 8.13 (d, 1H, J = 2.2 Hz), 7.85 (dd, 1H, J = 8.3, 2.2), 7.77 (broad, 1H), 7.66 (d, 1H, J = 8.3).

B. 2-amino-4-chlorobenzamide

A suspension of 2-nitro-4-chloro benzamide (2 g, 10 mmol), prepared as in Part A, in acetic acid (30 mL) is treated portionwise with zinc dust (2.6 g, 40 mmol) and stirred vigorously for 15h. The reaction mixture is diluted with CH_2Cl_2 (250 mL) and made basic with 2N NaOH. The organic layer is washed with H_2O (1 x 150 mL), brine (1 x 150 mL), dried (Na_2SO_4), and concentrated. The residue is purified by recrystallization from DMF to afford 2-amino-4-chlorobenzamide as a pale orange solid (570 mg).

^1H NMR (DMSO-d6) δ7.77 (broad, 1H, 7.52 (d, 1H, J = 8.6 Hz), 7.14 (broad, 1H), 6.81 (broad, 2H), 6.72 (d, 1H, J = 2.2 Hz), 6.47 (dd, 1H, J = 8.5, 2.2 Hz).

C. 7-chloro-2-phenyl-3H-quinazolin-4-one

A mixture of 2-amino-4-chlorobenzamide (500 mg, 2.9 mmol), prepared as in Part B, benzaldehyde (295 mL, 2.9 mmol) and $NaHSO_3$ (483 mg, 4.64 mmol) in dimethylacetamide (10 mL) is heated at 150 C for 2h. The mixture is allowed to cool, and poured into H_2O (50 mL). The resulting solid is collected by filtration and recrystallized from DMF, to afford the title compound as a tan solid (334 mg).

^1H NMR (DMSO-d6) δ 8.07 (m, 3H), 7.71 (d, 1H, J = 1.4 Hz), 7.47 (m, 4H).5

Intermediate 53

2-cyclohexyl-3H-quinazolin-4-one

A mixture of o-aminobenzamide (12.14g, 89.2 mmol), cyclohexane carboxaldehyde (10g, 89.2 mmol), and $NaHSO_3$ (14g, 134 mmol) in dimethylacetamide (120 mL) is heated at 150 C for 2h. The mixture is allowed to cool, then poured into H_2O (750 mL). The resulting solid is collected, washed with H_2O (2 x 200 mL), EtOH (2 x 200 mL) and Et_2O (2 x 200 mL) and dried *in vacuo* to afford the title compound as a tan solid (13.5 g).
^1H NMR (DMSO-d6) δ12.08 (s, 1H), 8.05 (dd, 1H, J = 8.1, 1.2 Hz), 7.75 (dt, 1H, J = 8.3, 1.4 Hz), 7.57 (d, 1H, J = 8.1 Hz), 7.43 (t, 1H, J = 7.8 Hz), 2.55 (tt, 1H, J = 11.7, 3.2 Hz), 1.88 (m, 2H), 1.77 (2H, m), 1.57 (m, 3H), 1.26 (m,3H).
C14H16N2O requires C: 73.66, H:7.06, N:12.27; found C:73.83, H: 7.01, N: 12.23.

Intermediate 54

2-(1H-pyrrol-2-yl)-3H-quinazolin-4-one

A mixture of o-aminobenzamide (10 g, 73.4 mmol), pyrrole 2-carboxaldehyde (6.98 g, 73.4 mmol), and $NaHSO_3$ (11.5 g, 110.1 mmol) in dimethylacetamide (120 mL) is heated at 150 C for 2h. The mixture is allowed to cool, then poured into H_2O (750 mL). The solution is extracted with $CHCl_3$ (3 x 200 mL) and the combined organic extracts are dried ($MgSO_4$) and concentrated to a tan solid. Recrystallization from DMF afforded the title compound as a tan solid (6.17 g).
^1H NMR (DMSO-d6) δ 12.24 (s, 1H), 11.76 (s, 1H), 8.10 (dd, 1H, J = 7.8, 1.2 Hz), 7.79 (dt, 1H, J = 7.1, 1.5 Hz), 7.63 (d, 1H, J = 8 Hz), 7.43 (t, 1H, J = 7.8 Hz), 7.34 (s, 1H), 7.06 (d, 1H, J = 1.2 Hz), 6.23 (m, 1H).
$C_{12}H_9N_3O$ requires C: 68.24, H:4.29, N: 19.89; found C:68.13, H: 19.92.

Intermediate 55

2-(3-chloro-4-fluoro-phenyl)-3H-quinazolin-4-one

A mixture of o-aminobenzamide (8.5 g, 62.3 mmol), 3-chloro-4-fluorobenzaldehyde (9.88 g, 62.3 mmol), and $NaHSO_3$ (9.7 g, 93.5 mmol) in dimethylacetamide (120 mL) is heated at 150 C for 2h. The mixture is allowed to

cool, then poured into H_2O (750 mL). The precipitated solid is collected, and dried in vacuo to afford the title compound as an off-white solid (16g).
^1H NMR (DMSO-d6) δ 8.54 (dd, 1H, J = 7.1, 2.2 Hz), 8.34 (m, 1), 8.28 (d, 1H, J = 7.8 Hz), 7.98 (dt, 1H, J = 8.3, 1.5 Hz), 7.88 (d, 1H, J = 7.5 Hz), 7.75 (t, 1H, J = 9.1 Hz), 7.67 (dt, 1H, J = 8.1, 1.2 Hz).
$C_{14}H_8N_2OFCl$ - 0.125 H2O requires C: 60.72, H: 3.00, N: 10.12; found C: 60.67, H: 3.03, N: 10.11.

Intermediate 56

5-chloro-2-phenyl-3H-quinazolin-4-one

A. 2-amino-6-chloro-N,N-diethyl benzamide

A solution of 2-amino-6-chlorobenzoic acid (8g, 46.6 mmol), diethylamine (14.5 mL, 139.8 mmol), and diisopropylethylamine (10 mL) in DMF (80 mL)is treated with PyBrop (26 g, 55.9 mmol), and stirred for 4h. The reaction mixture is partitioned between EtOAc and saturated aqueous $NaHCO_3$. The organic layer is washed with 1N HCl, H_2O, dried ($MgSO_4$) and concentrated to a yellow solid. The solid is purified by chromatography on silica using 50:50 EtOAc : Hexane as eluent to afford 2-amino-6-chloro-N,N-diethyl benzamide as an orange solid (5.7g).
^1H NMR (DMSO-d6) δ 7.01 (t, 1H, J = 7.8 Hz), 6.61 (m, 2H), 5.06 (s, 2H), 3.63 (m, 1H), 3.28 (m, 1H), 3.09 (q, 2H, J = 7.4 Hz), 1.13 (t, 3H, J = 7.1 Hz), 1.00 (t, 3H, J = 7.0 Hz).
$C_{11}H_{15}N_2OCl$ - 0.125 H_2O requires C:57.7, H: 6.71, N: 12.24; found C: 57.65, H: 6.60, N: 12.27.

B. 5-chloro-2-phenyl-3H-quinazolin-4-one

A solution of LDA (7 mL of a 1.5 M solution in cyclohexane, 10.5 mmol) in THF (20 mL) is cooled to -30 C and treated with a solution of 2-amino-6-chloro-N,N-diethyl benzamide (2.39 g, 10.5 mmol), prepared as in Part A, in THF (10 mL)

dropwise. A solution of benzonitrile (1.2 mL, 11.6 mmol) in THF (5 mL) is then added over a period of 5 minutes. The mixture is allowed to warm to 23 C and then heated at reflux for 20 min. After cooling, water (60 mL) is added and the pH of the mixture is adjusted to between 5 and 6 by the addition of NH_4Cl The precipitated solid is removed by filtration, washed with H_2O, and recrystallized from DMF to afford the title compound as an off-white solid (1g, 37%).
^1H NMR (DMSO-d6) δ 8.30 (m, 2H), 7.84 (m, 2H), 7.68 (m, 4H).
$C_{14}H_9N_2OCl$ requires C: 65.51, H: 3.53, N: 10.91, found C: 65.68, H: 3.39, N: 10.92.
FAB MS m/z 257 (MH+)

Intermediate 57

6-methoxy-2-phenyl-3H-quinazolin-4-one

A. 2-amino-5-methoxy-N,N-diethyl benzamide

A solution of 2-amino-5-methoxy benzoic acid (3.1 g, 18.5 mmol) in DMF (15 mL) is treated with diisopropylethylamine (6.4 mL, 37 mmol), diethylamine (1.9 mL, 18.5 mmol) and BOP reagent (8.2 g, 18.5 mmol) and stirred at 23 C for 15h. The reaction mixture is diluted with EtOAc (150 mL) and H_2O (150 mL). The organic layer is washed with saturated aqueous $NaHCO_3$ (100 mL) and brine (100 mL), dried (Na_2SO_4) and concentrated to a reddish brown oil. The oil is purified by chromatography on silica using 80:20 EtOAc : Hexane as eluent to afford 2-amino-5-methoxy-N,N-diethyl benzamide as a red oil 3.8g).
^1H NMR (DMSO-d6) d 6.69 (m, 2H), 6.52 (d, 1H, J = 2.7 Hz), 4.48 (s, 2H), 3.63 (s, 3H), 3.28 (m, 4H), 1.06 (m, 6H).

B. 6-methoxy-2-phenyl-3H-quinazolin-4-one

A solution of LDA (3.6 mL of a 1.5 M solution in cyclohexane, 5.4 mmol) in THF (10 mL) is cooled to -30 C and treated with a solution of 2-amino-5-methoxy-N,N-diethyl benzamide (1.2 g, 5.4 mmol), prepared as in Part A, in THF (5 mL)

dropwise. A solution of benzonitrile (0.6 mL, 5.9 mmol) in THF (3 mL) is then added over a period of 5 minutes. The mixture is allowed to warm to 23 C and then heated at reflux for 20 min. After cooling, water (60 mL) is added and the pH of the mixture is adjusted to between 5 and 6 by the addition of NH_4Cl The precipitated solid is removed by filtration, washed with H_2O, and recrystallized from DMF to afford the title compound as an off-white solid (0.5 g).

^1H NMR (DMSO-d6) δ 8.28 (m, 2H), 7.83 (d, 1H, J = 9.1 Hz), 7.68 (m, 4H), 7.57 (dd, 1H, J = 8.8, 2.9 Hz), 4.02 (s, 3H).

FAB MS m/z 253 (MH+).

Intermediate 58

4-[4[(2-phenyl-quinazolin-4-yl)-piperazin-1-yl]-butyraldehyde

A. 4-[4-[(2-phenyl-quinazolin-4-yl)-piperazin-1-yl]-butan-1-ol

A suspension of 2-phenyl-4-piperazin-1-yl-quinazoline hydrochloride (5g, 13.8 mmol), 4-bromobutan-1-ol (3 mL, 16.6 mmol), K_2CO_3 (7.63g, 55.2 mmol), and Et_3N (3 mL) in CH_3CN (15 mL) and dioxane (20 mL) is heated at 90 C for 15h. The solid is removed by filtration, and the solvent evaporated. The residue is purified by chromatography on silica using 5% MeOH:CH_2Cl_2 as eluent to afford 4-[4[(2-phenyl-quinazolin-4-yl)-piperazin-1-yl]-butan-1-ol as an off white solid (3g).

^1H NMR ($CDCl_3$) δ 8.40 (m, 2H), 7.83 (d, 1H, J = 7.9 Hz), 7.73 (d, 1H, J = 7.6 Hz), 7.58 (dt, 1H, J = 7.1, 1.2 Hz), 7.32 (m, 4H), 3.80 (m, 4H), 3.49 (m, 2H), 2.62 (m, 4H), 2.37 (m, 2H), 1.59 (m, 4H).

B. 4-[4[(2-phenyl-quinazolin-4-yl)-piperazin-1-yl]-butyraldehyde

A mixture of 4-[4-(2-phenyl-quinazolin-4-yl)-piperazin-1-yl]-butan-1-ol (700 mg, 1.93 mmol), prepared as in Part A, N-methyl morpholine N-oxide (340 mg, 2.9 mmol), and powdered 4 angstrom molecular sieves (1g) in CH_2Cl_2 (4 mL) under N_2 and at 23 C is treated with solid tetrapropylammoniumperruthenate (35 mg, 0.1

mmol). After 5h, the mixture is placed on a plug of silica, and eluted with EtOAc to afford the title compound as a white solid (466 mg).
^{1}H NMR ($CDCl_3$) δ 9.79 (s, 1H), 8.55 (m, 2H), 7.95 (d, 1H, J = 8.3 Hz), 7.85 (d, 1H, J = 8.3 Hz), 7.70 (t, 1H, J = 7.1 Hz), 7.46 (m, 3H), 7.38 (t, 1H, J = 7.3 Hz), 3.83 (m, 4H), 2.64 (m, 4H), 2.47 (dt, 2H, J = 6.9, 1.2 Hz), 2.41 (t, 2H, J = 6.8 Hz), 1.86 (m, 2H).

Intermediate 59

5-(3-Chloro-propyl)-2-methoxy-benzenesulfonamide

Chlorosulfonic acid (22 mL, 329 mmol) is added slowly via an addition funnel to neat 3-(4-methoxyphenyl)propyl chloride (8.6 g, 47 mmol) which is chilled at 0°C in an ice bath. After 45 min the solution is slowly poured with stirring into ice water. The mixture is then extracted with ethyl acetate. The combined organic layers are dried over magnesium sulfate, filtered and concentrated to a brown oil. Ammonia is then condensed into a solution of the brown oil and dioxane (30 mL) via a coldfinger. The reaction is stirred at room temperature for 16 h and is then filtered. The white solid that formed is washed with ethyl acetate. The filtrate is then extracted with saturated sodium bicarbonate solution, dried with magnesium sulfate, filtered and concentrated to give a pale yellow solid which is recrystallized from a hot methanol : ethyl acetate : hexane mixture (1:4:5) to give the title compound (5.8 g):
^{1}H NMR (DMSO-d_6) δ 7.55 (d, 1H, *J* = 2 Hz), 7.41 (dd, 1H, *J* = 1, 9 Hz), 7.13 (d, 1H, *J* = 8 Hz), 7.02 (s, 2H), 3.85 (s 3H), 3.59 (t, 2H, *J* = 7 Hz), 2.68 (t, 2H, *J* = 8 Hz), 1.95 (p, 2H, *J* = 7 Hz);
FAB MS *m / z* found 264 (MH^+).

Intermediate 60

5-(2-Chloro-ethyl)-2-methoxy-N-methyl-benzenesulfonamide

Chlorosulfonic acid (28 mL, 413 mmol) is added dropwise via an addition funnel to stirring neat 2-(4-methoxyphenyl)ethyl chloride (8.8 mL, 59 mmol) which is

chilled to 0°C in an ice bath. After 1 h the reaction mixture is poured very slowly into stirring ice water. The water mixture is then extracted with ethyl acetate. The organic layers are combined, dried with magnesium sulfate, filtered and concentrated to yield 5-(2-chloro-ethyl)-2-methoxy-benzenesulfonyl chloride as a yellow oil. Next aqueous methylamine (14 mL, 140 mmol) is added dropwise via an addition funnel to a solution of 5-(2-chloro-ethyl)-2-methoxy-benzenesulfonyl chloride (7.6 g, 28 mmol) in dioxane (25 mL). The reaction mixture is stirred at room temperature for 1.5 h and is then heated at 70°C for 1 h. Upon cooling, saturated sodium bicarbonate solution is added, and the mixture is extracted with ethyl acetate. The organic layers are combined, dried with magnesium sulfate, filtered, and concentrated to yield a yellow oil which is then purified by silica gel chromatography using an eluent of methanol:methylene chloride (1:9) to give the title compound as a pale yellow solid (4.8 g):
^{1}H NMR (DMSO-d$_6$) δ 7.61 (d, 1H, J = 2 Hz), 7.46 (dd, 1H, J = 2, 9 Hz), 3.89-3.79 (m, 5H), 3.01 (t, 2H, J = 7 Hz), 2.37 (d, 3H, J = 5 Hz);
FAB MS m/z found 264 (MH^+).

Intermediate 61

5-(2-Chloro-ethyl)-methoxy-N,N-dimethyl-benzenesulfonamide

Aqueous dimethylamine (20 mL, 140 mmol) is added dropwise via an addition funnel to a solution of 5-(2-chloro-ethyl)-2-methoxy-benzenesulfonyl chloride (7.6 g, 28 mmol). The reaction mixture is stirred at room temperature for 45 min and is then heated at 70°C for 1 h. Upon cooling, saturated sodium bicarbonate solution is added and the mixture is extracted with ethyl acetate. The combined organic layers are then dried with magnesium sulfate, filtered and concentrated to a yellow oil. The yellow oil is purified by silica gel chromatography using an eluant of methanol : methylene chloride (1:9) to give the title compound (1.9 g):
^{1}H NMR (DMSO-d$_6$) δ 7.63 (d, 1H, J = 2 Hz), 7.54 (dd, 1H, J = 3, 9 Hz), 3.88-3.79 (m, 5H), 3.01 (t, 2H, J = 6 Hz), 2.69 (s, 6H);
FAB MS m/z found 278 (MH^+).

Intermediate 62

3-(2-chloro-ethoxy)-benzamide

1-Bromo-2-chloroethane (3.0 mL, 36 mmol) and potassium carbonate (3.7 g, 36 mmol) are added to a stirring solution of 3-hydroxybenzamide (2.5 g, 18 mmol) in dioxane (13 mL). The mixture is refluxed for 5 h, then cooled to room temperature and diluted with sodium bicarbonate solution. The mixture is washed with chloroform and the organic layers are combined and concentrated to give the the title compound (1.7 g):
^{1}H NMR ($CDCl_3$) δ 7.01 (t, 1H, J = 8 Hz), 6.57 (d, 2H, J = 8 Hz), 4.21 (t, 2H, J = 6 Hz), 3.85 (s, 6H), 3.76 (t, 2H, J = 7 Hz);
FAB MS m/z found 200 (MH+)

Intermediate 63

3-[4-(2-Phenyl-quinazolin-4-yl)-piperazin-1-yl]-propylamine

A stirred solution of 2-{3-[4-(2-phenyl-quinazoli-4-yl)-piperazin-1-yl]-propyl}-isoindole-1,3 dione (16.79 g, 35 mmol), prepared as in Example 72, in absolute ethanol (350 mL) is warmed and hydrazine hydrate (4.4 mL, 140 mmol) is added. The reaction mixture is refluxed for 4 h. After cooling, the mixture is concentrated. The residue is partitioned between sodium bicarbonate solution and chloroform. The sodium bicarbonate layer is washed with chloroform. The organic layers are combined, dried over sodium sulfate, filtered and concentrated. The residue is purified by silica gel chromatography using an eluant of methanol:methylene chloride (1:9 to 2:3 with 0.1% to 3.0% ammonium hydroxide) to give the title compound (10.58 g):
^{1}H NMR (DMSO-d_6) δ 8.47-8.44 (m, 2H), 7.97 (d, 1H, J = 8 Hz), 7.85 (d, 1H, J = 8 Hz), 7.80-7.76 (m, 1H), 7.50-7.47 (m, 4H), 3.81-3.79 (m, 4H), 2.64-2.55 (m, 6H), 2.36 (t, 2H, J = 7 Hz), 1.54 (p, 2H, J = 7 Hz);
FAB MS m/z found 348 (MH^+).

Intermediate 64

2-[-(2-Phenyl-quinazolin-4-yl)-piperazin-1-yl]-ethylamine dimaleate

A. 2-{2-[4-(2-Phenyl-quinazolin-4-yl)-piperazin-1-yl]-ethyl}-isoindole-1,3-dione

N-(2-Bromoethyl)phthalamide (15.0 g, 59 mmol), potassium carbonate (24.5 g, 177 mmol) and sodium iodide (4.42 g, 30 mmol) are added to a stirring solution of 2-phenyl-4-piperazine-1-yl-quinazoline (17.27 g, 59 mmol). The reaction mixture is refluxed for 16 h. After cooling, the mixture is concentrated and the residue is partitioned between water and ethyl acetate. The aqueous layer is washed with ethyl acetate. The organic layers are combined, dried with magnesium sulfate, filtered and concentrated. The resulting white solid is triturated in ethyl acetate and then filtered to give 2-{2-[4-(2-phenyl-quinazolin-4-yl)-piperazin-1-yl]-ethyl}-isoindole-1,3-dione (19.6 g):
^{1}H NMR (DMSO-d6) δ 8.46-8.44 (m, 2H), 7.97 (d, 1H, J = 8 Hz), 7.88-7.76 (m, 6H), 7.51-7.46 (m, 4H), 3.76-3.73 (m, 6H), 2.68-2.65 (m, 4H), 2.61 (t, 2H, J = 6 Hz); FAB MS m/z found 464 (MH^+).
Anal. Calcd. for $C_{28}H_{25}N_5O_2$: C,54.16; H, 4.12; N, 9.87. Found: C, 54.31; H, 4.12; N, 9.86.

B. 2-[-(2-Phenyl-quinazolin-4-yl)-piperazin-1-yl]-ethylamine dimaleate

Hydrazine hydrate (4.65 mL, 148 mmol) is added to a stirring solution of 2-{2-[4-(2-phenyl-quinazolin-4-yl)-piperazin-1-yl]-ethyl}-isoindole-1,3-dione (17.30 g, 37 mmol), prepared as in Part A, in absolute ethanol (370 mL). The reaction mixture is refluxed for 4 h. After cooling, the mixture is concentrated and the residue is dissolved in sodium bicarbonate solution which is in turn washed with chloroform. The chloroform layers are combined, dried over sodium sulfate, filtered and concentrated. The residue is purified by silica gel chromatography with the eluant methanol : methylene chloride (1:9 to 3:7, with 1% ammonium hydroxide) to give the product. The maleate salt is made by dissolving the product in a minimal amount of

hot ethyl acetate and adding maleic acid (557 mg, 4.8 mmol) which had been dissolved in methanol (0.5 mL). Upon cooling, the solid which formed is filtered and washed wtih ethyl acetate to give the title compound (8.8 g):
^{1}H NMR (DMSO-d6) δ 8.47-8.44 (m, 2H), 7.97 (d, 1H, J = 8 Hz), 7.85 (d, 1H, J = 8 Hz), 7.50-7.46 (m, 4H), 3.81-3.79 (m, 4H), 2.64 (t, 2H, J = 7 Hz) 2.60-2.58 (m, 4H), 2.35 (t, 2H, J = 7 Hz);
FAB MS m/z found 334 (MH^+).

Intermediate 65

2-[5-(2-Chloro-ethyl)-2-methoxy-benzenesulfonylamino]-acetamide

5-(2-Chloro-ethyl)-2-methoxy-benzenesulfonyl chloride (5.78 g, 21.5 mmol) was dissolved in dioxane (72 mL). To this solution was added glycinamide hydrochloride (4.75 g, 42.9 mmol) and N,N-diisopropylethylamine (7 mL, 42.9 mmol) with stirring at room temperature for 24 h. The solution was diluted with ethyl acetate (100 mL) and washed with 1M H_3PO_4 (2 x 50 mL), H_2O (1 x 50 mL), sat $NaHCO_3$, (1 x 50 mL,) brine (1 x 50 mL). The organic phase was dried with Na_2SO_4, filtered and the volatiles concentrated to a white solid. The solid was collected on a Buchner funnel by vacuum filtration and washed with ether to provide the title compound (5.33 g):
Rf = 0.13 ethyl acetate in hexanes (3:1);
^{1}H NMR (400 MHz, DMSO-d6) δ 7.60 (d, 1H, J = 2.2 Hz), 7.48 (dd, 1H, J = 8.6, 2.2 Hz), 7.18-7.10 (m, 4H), 3.84 (s, 3H), 3.80 (t, 2H, J = 6.8 Hz), 3.37 (d, 2H, J = 4.2 Hz), 2.99, (t, 2H, J = 6.8 Hz).

Intermediate 66

2-Phenyl-4-piperazin-1-yl-quinazoline

Piperazine (128 g, 1.48 mole) was taken up in 1.750 L of tetrahydrofuran and the solution heated to near reflux to dissolve the piperazine. To this solution was added 2-chloro-4-phenyl quinazoline (38.5 g, 160 mmol) with an immediate increase

in the turbidity of the solution. After stirring for 14 h the reaction mixture was concentrated and taken up in methylene chloride (1L) then washed with water (5 x 150 mL), and brine (1 x 150 mL). The solution was concentrated after drying and filtering to provide the title compound as a white solid (38.6 g):
Rf = 0.36 methanol in methylene chloride (1:20) with 1% ammonium hydroxide; ^{1}H NMR (DMSO-d_6) δ 8.48 (m, 2H), 8.30 (s, 1H), 8.0 (d, 1H, J = 8 Hz), 7.83 (m, 2H), 7.50 (m, 4H), 3.8 (s, 4H), 3.09 (s, 4H)

Intermediate 67

4-(2-Chloro-ethyl)-benzamide

4-(2-Chloroethyl)-benzoic acid (10.08 g, 54.6 mmol) was slurried in methylene chloride (182 mL) and to the slurry was added dimethylformamide (4 drops) and portionwise addition of oxalyl chloride (5.3 mL, 60.0 mmol) over 1.5 h then stirring was continued for an additional 2 h. The turbid solution becomes clear as the oxalyl chloride is added. Concentrated ammonium hydroxide (100 mL) was then cautiously added with stirring continued for 16 h. The mixture was diluted with water (100 mL) and the phases separated. The aqueous phase was extracted with methylene chloride (2 x 75 mL). The combined organic phases were dried (Na_2SO_4), filtered and the volatiles concentrated to furnish the title compound (8.63 g) as a white solid:
Rf = 0.24 (1:1 ethyl acetate in hexanes);
^{1}H NMR (300 MHz, DMSO-d_6) δ 7.93 (bs, 1H), 7.81 (d, 2H, J = 8.0 Hz), 7.33 (d, 2H, 8.3 Hz), 3.86 (t, 2H, J = 6.8 Hz), 3.05 (t, 2H, J = 6.8 Hz).

Intermediate 68

4-(3,3-Dimethyl-piperazin-1-yl)-2-phenyl-quinazoline

A solution of 4-chloro-2-phenyl-quinazoline (2.31 g, 9.6 mmol) in THF (50ml) was treated with 2,2-dimethylpiperazine (3.30 g, 28.8 mmol) Miyamoto,T.; Matsumoto,J.; Chiba,K.; Egawa,H.; Shibamori,K.;Minamida,A.;Nishimura,Y.; Okada,H.; Kataoka,M.;

J.Med.Chem. (1990),33 (6), 1645-56. and triethylamine (1.45 g,14.4mmol), and heated to 60°C for 3 hr. The mixture was cooled and concentrated.The residue was diluted with satur'd Na_2CO_3 (25 ml) and extracted with ethyl acetate. The organic phases were combined and dried over $MgSO_4$, filtered and concentrated affording the title compound (2.80 g):
^1H ($CDCl_3$) δ 8.57 (d, 2H),7.91 (2d,2H), 7.75 (t,1H), 7.367.49 (m,4H), 3.77 (m,2H), 3.58 (s,2H), 3.20 (m,2H),1.22 (s,6H):
FAB MS 319 (MH+).

Intermediate 69

4-(3,8-Diaza-bicyclo[3.2.1] oct-8-yl)-2-phenyl-quinazoline

A. 4-(3-Benzyl-3,8-diaza-bicyclo[3.2.1]oct-8-yl)-2-phenyl-quinazoline

A solution of 4-chloro-2-phenyl-quinazoline (398 mg,1.65mmol), in THF (60ml) was treated with 3-benzyl-3,8-diazabicyclooctane [3.2.1] (280 mg,1.38 mmol),Cignarella, G *et al,* J.Org.Chem.1961, 26, 1502 and triethylamine (698 mg, 6.9 mmol) and heated at 65 C for 4.5 hr.The mixture was cooled and concentrated.The crude residue was diluted with Na_2CO_3 (10ml) and extracted with ethyl acetate.The organic phase was dried over $MgSO_4$, filtered and concentrated to give crude which was column purified by silica gel chromatography using 50:50 hexane:ethyl acetate which afford 4-(3-Benzyl-3,8-diaza-bicyclo[3.2.1]oct-8-yl)-2-phenyl-quinazoline (260 mg)
^1H($CDCl_3$) δ 8.55 (d,2H),7.98 (d,2H), 7.25-7.71 (m,10H), 4.9(bs,2H), 3.59 (s,2H), 2.85 (d,2H), 2.65(d,2H), 2.11 (m,2H), 1.91(m,2H):
FAB MS 407 (MH+).

B. 4-(3,8-Diaza-bicyclo[3.2.1] oct-8-yl)-2-phenyl-quinazoline

A solution of 4-(3-benzyl-3,8-diaza-bicyclo[3.2.1]oct-8-yl)-2-phenyl-quinazoline(260mg,.63mmol) in (10ml), prepared as in Part A, methanol and (3.35ml) H_2O under N_2 was treated with 10% Pd/carbon (125 mg) followed by

ammonium formate (158.9 mg,2.52 mmol). The mixture was heated at reflux for 2.5 hr.The reaction mixture was concentrated to a residue then stripped (3X25ml) with toluene to remove water.The residue was dried affording the title compound (200 mg)

^{1}H (CDCl3) δ 8.3 (m,1H) 7.71 (t,1H), 7.55 (t,1H),7.23 (m,4H), 7.0 (m,1H), 6.92 (m,1H), 4.71 (s,2H), 3.25 (bd,2H), 2.91(d,2H), 2.38 (s,1H), 2.05 (s,1H), 1.91 (s,2H).

Example 1

5-{2-[4-(2-Phenyl-quinazolin-4-yl)-[1,4]diazepan-1-yl]-ethyl}-2-methoxy-benzenesulfonamide bistrifluoroacetate

Sodium iodide (15.6 mg, 0.10 mmol) is added to 4-[1,4]Diazepan-1-yl-2-phenyl-quinazoline (317.7 mg, 1.04 mmol), prepared as in Intermediate 1, in ethanol (4 ml). Then, potassium carbonate (144.3 mg, 1.04 mmol) is added to the mixture. Finally, 5-(2-chloro-ethyl)-2-methoxy-benzenesulfonamide (260.6 mg, 1.04 mmol) is added to the mixture and it is heated at 150°C in a sealed tube for 15 h. Water is added and the reaction is extracted with ethyl acetate. The combined organic layers are dried with magnesium sulfate and concentrated. The residue is purified by silica gel chromatography using methanol:ethyl acetate (1:9) as eluant, followed by reverse phase HPLC using acetonitrile:water (5% to 40% gradient over 30 min) as eluant to give the title compound (70.9 mg):

RP HPLC 19.7 min;

^{1}H NMR (CD_3OD) δ 8.37 (d, 1H, J = 8 Hz), 8.33-8.30 (m, 2H), 8.11-8.01 (m, 2H), 7.81-7.75 (m, 3H), 7.72-7.66 (m, 2H), 7.50 (dd, 1H, J = 9, 2 Hz), 7.16 (d, 1H, J = 9 Hz), 4.49-4.45 (m, 4H), 3.95 (s, 3H), 4.02-3.45 (m, 4H), 3.46-3.40 (m, 2H), 3.14-3.09 (m, 2H), 2.58-2.55 (m, 2H);

High resolution FAB MS *m/z* found 518.2233 (MH^+), $C_{28}H_{32}N_5O_3S$ requires 518.2226.

Anal. Calcd. for $C_{32}H_{33}F_6N_5O_7S$: C, 51.54; H, 4.46; N, 9.39. Found: C, 51.78; H, 4.73; N, 9.64.

Example 2

5-{2-[4-(2-Phenyl-quinazolin-4-ylamino)-piperidin-4-yl]-ethyl}-2-methoxy-benzenesulfonamide bistrifluoroacetate

Synthesized in a manner similar to Example 1, using 1-(2-phenyl-quinazolin-4-yl)-piperidin-4-yl-amine (618.1 mg, 2.03 mmol), prepared as in Intermediate 2, and 5-(2-chloro-ethyl)-2-methoxy-benzenesulfonamide (507.1 mg, 2.03 mmol) to give the title compound (431.3 mg).

RP HPLC 20.7 min;

^{1}H NMR (CD_3OD) δ 8.50 (d, 1H, J = 8 Hz), 8.37-8.34 (m, 2H), 8.08 (t, 1H, J = 7 Hz), 7.99 (d, 1H, J = 8 Hz), 7.83-7.76 (m, 3H), 7.69 (t, 2H, J = 8 Hz), 7.54 (dd, 1H, J = 9, 2 Hz), 7.20 (d, 1H, J = 8 Hz), 5.03-4.98 (m, 1H), 3.98 (s, 3H), 3.93-3.79 (m, 2H), 3.44-3.36 (m, 2H), 3.18-3.08 (m, 2H), 2.57-2.42 (m, 3H), 2.31-2.12 (m, 3H);

High resolution FAB MS *m/z* found 518.2255 (MH^+), $C_{28}H_{32}N_5O_3S$ requires 518.2226.

Example 3

5-{2-[2-Methyl-4-(2-phenyl-quinazolin-4-yl)-piperazin-1-yl]-ethyl}-2-methoxy-benzenesulfonamide bistrifluoroacetate

Synthesized in a manner similar to Example 1, using 4-(3-methyl-piperazin-1-yl)-2-phenyl-quinazoline (628.8 mg, 2.07 mmol), prepared as in Intermediate 3, and 5-(2-chloro-ethyl)-2-methoxy-benzenesulfonamide (515.9 mg, 2.07 mmol) to give the title compound (297.3 mg).

RP HPLC 19.9 min;

^{1}H NMR (CD_3OD) δ 8.38 (dd, 2H, J = 7, 2 Hz), 8.26 (d, 1H, J = 8 Hz), 8.06 (m, 2H), 7.83-7.63 (m, 5H), 7.56 (dd, 1H, J = 9, 2 Hz), 7.20 (d, 1H, J = 9 Hz), 4.88-4.65 (m, 1H), 4.40-4.25 (m, 2H), 3.98 (s, 3H), 3.94-3.81 (m, 2H), 3.66-3.55 (m, 2H), 3.49-3.36 (m, 1H), 3.24-3.02 (m, 3H), 1.55 (d, 3H, J = 7 Hz);

High resolution FAB MS *m/z* found 518.2224 (MH^+), $C_{28}H_{32}N_5O_3S$ requires 518.2226.

Example 4

2-(2-Phenyl-quinazolin-4-yl)-1,2,3,4,6,7,12,12a-octahydro-benzo[4,5]azepino[1,2-a]pyrazine bistrifluoroacetate

N,N-di-*iso*-propylethyl amine (0.10 ml, 0.571 mmol) is added to a solution of 1,2,3,4,6,7,12,12a-octahydro-benzo[4,5]azepino[1,2-a]pyrazine (28.9 mg, 0.143 mmol, Dixit, V. M. *et al, Ind. J. Chem.* 1975, *13*, 893.) in ethanol (4.8 ml). Then, 4-Chloro-2-phenyl-quinazoline (34.4 mg, 0.143 mmol) is added and the solution is heated at 150°C in a sealed tube for 16 h. The solution is cooled, saturated sodium carbonate is added, and the mixture is extracted with ethyl acetate. The combined organic layers are dried with magnesium sulfate and concentrated. The residue is purified by silica gel chromatography using ethyl acetate as eluant, followed by reverse phase HPLC using acetonitrile:water (5% to 40% gradient over 30 min) as eluant to give the title compound (70.4 mg):
RP HPLC 23.0 min;
^{1}H NMR (CD_3OD) δ 8.39-8.36 (m, 2H), 8.25 (d, 1H, J = 8 Hz), 8.09-8.03 (m, 2H), 7.80-7.72 (m, 1H), 7.71-7.61 (m, 3H), 7.34-7.31 (m, 1H), 7.28-7.23 (m, 3H), 5.08 (dd, 2H, J = 27, 15 Hz), 4.06 (t, 1H, J = 12 Hz), 3.94 (t, 1H, J = 12 Hz), 3.84 (dd, 1H, J = 13, 6 Hz), 3.76 (d, 1H, J = 13 Hz), 3.62 (m, 1H), 3.54-3.43 (m, 3H), 3.22-3.05 (m, 3H);
High resolution FAB MS *m/z* found 407.2239 (MH^+), $C_{27}H_{27}N_4$ requires 407.2236.

Example 5

2-(2-Phenyl-quinazolin-4-yl)-1,2,3,4,6,11,12,12a-octahydro-benzo[5,6]azepino[1,2-a]pyrazine bistrifluoroacetate

Synthesized in a manner similar to Example 4, using 1,2,3,4,6,11,12,12a-octahydro-benzo[5,6]azepino[1,2-a]pyrazine (27.9 mg, 0.138 mmol, Dixit, *et al, Ind. J. Chem.* 1975, *13*, 893.) and 4-Chloro-2-phenyl-quinazoline (33.2 mg, 0.138 mmol) to give the title compound (55.3 mg).
RP HPLC 22.0 min;

^{1}H NMR (CD_3OD) δ 8.38-8.36 (m, 2H), 8.26 (d, 1H, J = 9 Hz), 8.12-8.06 (m, 2H), 7.83-7.66 (m, 4H), 7.48-7.30 (m, 4H), 5.16-4.86 (m, 2H), 4.61 (ABq, 2H, J_{AB} = 14 Hz, $\Delta\nu_{AB}$ = 111 Hz), 4.25-3.61 (m, 5H), 3.30-3.01 (ABX, 2H), 2.48-2.37 (m, 1H), 1.99-1.82 (m, 1H);

High resolution FAB MS *m/z* found 407.2239 (MH^+), $C_{27}H_{27}N_4$ requires 407.2236.

Example 6

5-{2-[3-(2-Phenyl-quinazolin-4-ylamino)-piperidin-1-yl]-ethyl}-2-methoxy-benzenesulfonamide

Synthesized in a manner similar to Example 4, using 5-[2-(3-amino-piperidin-1-yl)-ethyl]-2-methoxy-benzenesulfonamide (625.1 mg, 1.99 mmol), prepared as in Intermediate 4, and 4-Chloro-2-phenyl-quinazoline (480.0 mg, 1.99 mmol) to give the title compound (586.8 mg).

^{1}H NMR ($CDCl_3$) δ 8.50 (dd, 2H, J = 8, 2 Hz), 7.86 (d, 1H, J = 8 Hz), 7.75 (d, 1H, J = 2 Hz), 7.68 (t, 1H, J = 8 Hz), 7.60-7.48 (m, 1H), 7.47-7.36 (m, 4H), 7.30 (dd, 1H, J = 8, 2 Hz), 6.83 (d, 1H, J = 9 Hz), 6.38 (br s, 1H), 5.22 (br s, 2H), 4.74 (m, 1H), 3.89 (s, 3H), 2.88-2.62 (m, 7H), 2.40-2.26 (m, 1H), 2.00-1.61 (m, 4H);

High resolution FAB MS *m/z* found 518.2227 (MH^+), $C_{28}H_{32}N_5O_3S$ requires 518.2226.

Example 7

5-{2-[3-(2-Phenyl-quinazolin-4-ylamino)-azepan-1-yl]-ethyl}-2-methoxy-benzenesulfonamide

Triethylamine (0.24 ml, 1.73 mmol) is added to a solution of 5-[2-(3-amino-azepan-1-yl)-ethyl]-2-methoxy-benzenesulfonamide (568.3 mg, 1.73 mmol), prepared as in Intermediate 5, in tetrahydrofuran (17 ml). Then, 4-Chloro-2-phenyl-quinazoline (417.7 mg, 1.73 mmol) is added and the solution is heated at reflux for 15 h. The solution is cooled, saturated sodium carbonate is added, and the mixture is extracted with ethyl acetate. The combined organic layers are dried with magnesium sulfate and concentrated. The residue is purified by silica gel

chromatography using methanol:ethyl acetate (1:19) as eluant to give the title compound (362.5 mg): RP HPLC 19.6 min;
^{1}H NMR ($CDCl_3$) δ 8.51-8.48 (m, 2H), 7.86 (d, 2H, *J* = 8 Hz), 7.75 (s, 1H), 7.66 (t, 1H, *J* = 8 Hz), 7.46-7.42 (m, 4H), 7.35 (t, 1H, *J* = 7 Hz), 7.24 (dd, 1H, *J* = 8, 2 Hz), 6.81 (d, 1H, *J* = 9 Hz), 6.76 (br s, 1H), 5.09 (s, 2H), 4.74 (s, 1H), 3.89 (s, 3H), 3.06-2.78 (m, 7H), 2.66-2.60 (m, 1H), 2.13-2.09 (m, 1H), 1.93-1.56 (m, 5H); High resolution FAB MS *m/z* found 532.2387 (MH^+), $C_{29}H_{34}N_5O_3S$ requires 532.2382. Anal. Calcd. for $C_{29}H_{34}N_5O_3S$: C, 63.36; H, 6.41; N, 12.74. Found: C, 63.72; H, 6.08; N, 12.50.

Example 8

5-[2-[3,5-Dimethyl-4-(2-phenyl-quinazolin-4-yl)-piperazin-1-yl]-ethyl]-2-methoxy-benzenesulfonamide trifluoroacetate

Synthesized in a manner similar to Example 7, using 5-[2-(3,5-dimethyl-piperazin-1-yl)-ethyl]-2-methoxy-benzenesulfonamide (1.03 g, 3.13 mmol), prepared as in Intermediate 6, and 4-Chloro-2-phenyl-quinazoline (502.6 mg, 2.09 mmol) to give the title compound (131.6 mg).
RP HPLC 19.7 min;
^{1}H NMR (CD_3OD) δ 8.50-8.44 (m, 3H), 8.10-8.03 (m, 2H), 7.84 (d, 1H, *J* = 2 Hz), 7.74 (t, 1H, *J* = 7 Hz), 7.61-7.54 (m, 4H), 7.21 (d, 1H, *J* = 8 Hz), 3.99 (s, 3H), 3.78-3.51 (m, 2H), 3.48-3.13 (m, 8H), 1.12 (br s, 6H);
High resolution FAB MS *m/z* found 532.2371 (MH^+), $C_{29}H_{34}N_5O_3S$ requires 532.2382.

Example 9

5-[2-[3-Methyl-4-(2-phenyl-quinazolin-4-yl)-piperazin-1-yl]-ethyl]-2-methoxy-benzenesulfonamide trifluoroacetate

Synthesized in a manner similar to Example 7, using 5-[2-(3-methyl-piperazin-1-yl)-ethyl]-2-methoxy-benzenesulfonamide (605.2 mg, 1.93 mmol), prepared as in

Intermediate 7, and 4-Chloro-2-phenyl-quinazoline (464.7 mg, 1.93 mmol) to give the title compound (873.2 mg).

RP HPLC 19.7 min;

^{1}H NMR (CD_3OD) δ 8.39-8.36 (m, 2H), 8.21 (d, 1H, J = 8 Hz), 8.11-8.05 (m, 2H), 7.82-7.64 (m, 5H), 7.52 (dd, 1H, J = 8, 2 Hz), 7.19 (d, 1H, J = 9 Hz), 5.49 (m, 1H), 5.03-4.90 (m, 1H), 4.14 (t, 1H, J = 12 Hz), 3.97 (s, 3H), 3.85-3.81 (m, 1H), 3.73-3.65 (m, 1H), 3.49-3.34 (m, 4H), 3.16-3.11 (m, 2H), 1.79 (d, 3H, J = 7 Hz); High resolution FAB MS *m/z* found 518.2245 (MH^+), $C_{28}H_{32}N_5O_3S$ requires 518.2225.

Example 10

5-{2-[1-(2-Phenyl-quinazolin-4-yl)-piperidin-1-ylamino]-ethyl}-2-methoxy-benzenesulfonamide trifluoroacetate

Synthesized in a manner similar to Example 1, using 1-(2-phenyl-quinazolin-4-yl)-piperadin-4-yl-amine (610.9 mg, 2.01 mmol), prepared as in Intermediate 8, and 5-(2-chloro-ethyl)-2-methoxy-benzenesulfonamide (250.6 mg, 1.00 mmol) to give the title compound (82.4 mg).

^{1}H NMR ($CDCl_3$) δ 8.30 (dd, 2H, J = 7, 1 Hz), 8.22 (d, 1H, J = 8 Hz), 8.06 (t, 1H, J = 8 Hz), 8.02 (dt, 1H, J = 6, 1 Hz), 7.88-7.74 (m, 3H), 7.67 (t, 2H, J = 7 Hz), 7.53 (dd, 1H, J = 8, 2 Hz), 7.20 (d, 1H, J = 9 Hz), 5.18-5.13 (m, 2H), 3.98 (s, 3H), 3.76-3.65 (m, 3H), 3.38-3.33 (m, 2H), 3.04 (t, 2H, J = 9 Hz), 2.46-2.42 (m, 2H), 2.01-1.92 (m, 2H);

High resolution FAB MS *m/z* found 518.2241 (MH^+), $C_{28}H_{32}N_5O_3S$ requires 518.2226.

Example 11

N 2-Benzyl-N 2-methyl-N 4-(2-Phenyl-quinazolin-4-yl)-pyridine-2,4-diamine trifluoroacetate

Synthesized in a manner similar to Example 7, using N-2-Benzyl-N 2-methyl-pyridine-2,4-diamine (489.9 mg, 2.30 mmol, Hertog, *et al, Eur. J. Pharmacol.* 1987,

142, 115.) and 4-Chloro-2-phenyl-quinazoline (34.4 mg, 0.143 mmol) to give the title compound (17.1 mg).
RP HPLC 15.7 min;
^{1}H NMR (CD_3OD) δ 8.47 (dd, 2H, *J* = 3, 1 Hz), 8.41 (s, 1H), 8.38 (d, 1H, *J* = 2 Hz), 8.03 (dt, 1H, *J* = 8, 1 Hz), 7.98 (dt, 1H, *J* = 3, 1 Hz), 7.91 (d, 1H, *J* = 7 Hz), 7.72 (dt, 1H, *J* = 7, 2 Hz), 7.53-7.46 (m, 2H), 7.41-7.31 (m, 5H), 7.24 (d, 2H, *J* = 8 Hz), 4.90 (s, 2H), 3.30 (s, 3H);
High resolution FAB MS *m/z* found 418.2032 (MH^+), $C_{27}H_{24}N_5$ requires 418.2032.

Example 12

N 2-Benzyl-N 2-methyl-N 5-(2-Phenyl-quinazolin-4-yl)-pyridine-2,5-diamine

N 2-Benzyl-N 2-methyl-pyridine-2,5-diamine (667.9 mg, 3.13 mmol), prepared as in Intermediate 9, is added to a solution of 4-Chloro-2-phenyl-quinazoline (502.5 mg, 2.09 mmol) in tetrahydrofuran (8.4 ml) and the solution is heated at 150°C in a sealed tube for 15 h. The solution is cooled, saturated sodium carbonate is added, and the mixture is extracted with ethyl acetate. The combined organic layers are dried with magnesium sulfate and concentrated. The residue is purified by silica gel chromatography using ethyl acetate:hexanes (2:3) as eluant and recrystalized from ethyl acetate:hexanes to give the title compound (609.7 mg):
RP HPLC 26.6 min;
^{1}H NMR ($CDCl_3$) δ 8.47 (d, 2H, *J* = 4 Hz), 8.41 (d, 1H, *J* = 2 Hz), 8.02 (dd, 1H, *J* = 9, 2 Hz), 7.94 (d, 1H, *J* = 8 Hz), 7.83 (d, 1H, *J* = 8 Hz), 7.73 (t, 1H, *J* = 8 Hz), 7.46-7.41 (m, 5H), 7.36-7.24 (m, 5H), 6.59 (d, 2H, *J* = 9 Hz), 4.82 (s, 2H), 3.10 (s, 3H);
^{13}C NMR ($CDCl_3$) δ 160.36, 157.86, 156.30, 150.92, 141.89, 138.61, 138.57, 133.22, 132.75, 130.12, 129.06, 128.52, 128.39, 128.29, 127.01, 126.92, 125.82, 124.72, 120.43, 113.70, 105.29, 53.52, 36.48;
High resolution FAB MS *m/z* found 418.2024 (MH^+), $C_{27}H_{24}N_5$ requires 418.2032.
Anal. Calcd. for $C_{27}H_{23}N_5$: C, 77.67; H, 5.55; N, 16.77. Found: C, 77.50; H, 5.59; N, 16.73.

Example 13

5-2-(Methyl-[3-(2-Phenyl-quinazolin-4-yl)-propyl]-amino)-ethyl)-2-methoxy-benzenesulfonamide trifluoroacetate

Synthesized in a manner similar to Example 1, using methyl-[3-(2-phenyl-quinazolin-4-yl)-propyl]-amine (89.3 mg, 0.32 mmol), prepared as in Intermediate 10, and 5-(2-chloro-ethyl)-2-methoxy-benzenesulfonamide (160.8 mg, 0.64 mmol) to give the title compound (55.1 mg).

^{1}H NMR (CD_3OD) δ 8.56-8.53 (m, 2H), 8.28 (d, 1H, J = 8 Hz), 8.08 (d, 1H, J = 8 Hz), 7.97 (dt, 1H, J = 7, 1 Hz), 7.78 (d, 1H, J = 8 Hz), 7.71 (dt, 1H, J = 7, 1 Hz), 7.52-7.45 (m, 4H), 7.14 (d, 1H, J = 9 Hz), 3.96 (s, 3H), 3.57-3.32 (m, 6H), 3.30-3.00 (m, 2H), 3.02 (s, 3H), 2.60-2.46 (m, 2H);

FAB MS *m/z* found 491 (MH^+).

Example 14

5-(2-{3-[Methyl-(2-phenyl-quinazolin-4-yl)-amino]-pyrrolidin-3-yl}-ethyl)-2-methoxy-benzenesulfonamide bistrifluoroacetate

Synthesized in a manner similar to Example 1, using methyl-(2-phenyl-quinazolin-4-yl)-pyrrolidin-3-yl-amine (159.1 mg, 0.52 mmol), prepared as in Intermediate 11, and 5-(2-chloro-ethyl)-2-methoxy-benzenesulfonamide (261.0 mg, 1.05 mmol) to give the title compound (98.3 mg).

RP HPLC 18.0 min;

^{1}H NMR (CD_3OD) δ 8.51 (d, 1H, J = 9 Hz), 8.34 (d, 2H, J = 9 Hz), 8.09-8.00 (m, 2H), 7.85-7.74 (m, 3H), 7.68 (t, 1H, J = 7 Hz), 7.59-7.56 (m, 1H), 7.18 (d, 1H, J = 9 Hz), 4.78-4.73 (m, 1H), 4.61-4.57 (m, 2H), 4.38-4.32 (m, 2H), 3.97 (s, 3H), 3.59-3.55 (m, 2H), 3.20-3.11 (m, 2H), 3.13 (s, 3H), 2.73 (m, 1H), 2.58-2.48 (m, 1H);

High resolution FAB MS *m/z* found 518.2217 (MH^+), $C_{28}H_{32}N_5O_3S$ requires 518.2226.

Example 15

5-{2-[3-Methyl-3-(2-phenyl-quinazolin-4-yl-amino)-pyrrolidin-1-yl]-ethyl}-2-methoxy-benzenesulfonamide bistrifluoroacetate

Sodium iodide (187.4 mg, 1.25 mmol) is added to (3-methyl-pyrrolidin-3-yl)-(2-phenyl-quinazolin-4-yl)-amine (380.7 mg, 1.25 mmol), prepared as in Intermediate 12, in ethanol (6 ml). Then, N,N-di-*iso*-propyl-ethyl-amine (0.87 ml, 5.00 mmol) is added to the mixture. Finally, 5-(2-chloro-ethyl)-2-methoxy-benzenesulfonamide (624.6 mg, 2.50 mmol) is added to the mixture and it is heated at 150°C in a sealed tube for 24 h. Water is added and the reaction is extracted with ethyl acetate. The combined organic layers are dried with magnesium sulfate and concentrated. The residue is purified by silica gel chromatography using methanol:ethyl acetate (1:7) as eluant, followed by reverse phase HPLC using acetonitrile:water (5% to 40% gradient over 30 min) as eluant to give the title compound (311.4 mg):
RP HPLC 20.1 min;
^{1}H NMR (CD_3OD) δ 8.55 (d, 1H, J = 8 Hz), 8.31-8.28 (m, 2H), 8.09 (t, 1H, J = 8 Hz), 8.01 (d, 1H, J = 8 Hz), 7.83-7.70 (m, 5H), 7.46 (dd, 1H, J = 9, 2 Hz), 7.12 (d, 1H, J = 9 Hz), 4.00-3.86 (m, 1H), 3.93 (s, 3H), 3.60-3.44 (m, 4H), 3.11-2.93 (m, 4H), 2.66-2.47 (m, 1H), 1.95 (s, 3H);
High resolution FAB MS *m/z* found 518.2213 (MH^+), $C_{28}H_{32}N_5O_3S$ requires 518.2226.
Anal. Calcd. for $C_{32}H_{33}F_6N_5O_7S$: C, 51.54; H, 4.46; N, 9.39. Found: C, 51.29; H, 4.59; N, 9.42.

Example 16

5-{2-[3,4-Dimethyl-3-(2-phenyl-quinazolin-4-yl-amino)-pyrrolidin-1-yl]-ethyl}-2-methoxy-benzenesulfonamide bistrifluoroacetate

Sodium iodide (189.3 mg, 1.26 mmol) is added to (3,4-dimethyl-pyrrolidin-3-yl)-(2-phenyl-quinazolin-4-yl)-amine (402.2 mg, 1.26 mmol), prepared as in Intermediate 13, in ethanol (6.3 ml). Then, N,N-di-*iso*-propyl-ethyl-amine (0.88 ml,

5.05 mmol) is added to the mixture. Finally, 5-(2-chloro-ethyl)-2-methoxy-benzenesulfonamide (630.8 mg, 2.53 mmol) is added to the mixture and it is heated at 150°C in a sealed tube for 20 h. Water is added and the reaction is extracted with ethyl acetate. The combined organic layers are dried with magnesium sulfate and concentrated. The residue is purified by silica gel chromatography using methanol:ethyl acetate (1:9) as eluant, followed by reverse phase HPLC using acetonitrile:water (5% to 40% gradient over 30 min) as eluant to give the title compound (636.2 mg):

RP HPLC 19.8 min;

^{1}H NMR (CD_3OD) δ 8.59 (d, 1H, J = 8 Hz), 8.26 (d, 2H, J = 7 Hz), 8.09 (t, 1H, J = 7 Hz), 8.00 (d, 1H, J = 8 Hz), 7.82-7.77 (m, 2H), 7.74-7.70 (m, 3H), 7.45 (d, 1H, J = 8 Hz), 7.12 (d, 1H, J = 9 Hz), 4.69 (m, 1H), 4.05 (m, 1H), 3.71 (m, 1H), 3.51 (m, 2H), 3.13 (m, 2H), 2.99 (m, 2H), 1.83 (s, 3H), 1.35 (d, 3H, J = 7 Hz);

High resolution FAB MS *m/z* found 532.2387 (MH^+), $C_{29}H_{34}N_5O_3S$ requires 532.2382.

Example 17

5-{2-[2,5-dimethyl-4-(2-phenyl-quinazolin-4-yl)-piperazin-1-yl]-ethyl}-2-methoxy-benzenesulfonamide

5-(2-Chloro-ethyl)-2-methoxy-benzenesulfonamide (0.25 g, 1.00 mmol) is added to a stirred solution of 4-(2,5-dimethyl-piperazin-1-yl)-2-phenyl-quinazoline (0.30 g, 0.95 mmol), prepared as in Intermediate 14, potassium carbonate (0.28 g, 2.00 mmol), and sodium iodide (0.02 g, 0.10 mmol) in acetonitrile (5 ml) and the solution heated to reflux for 16 h. Saturated sodium carbonate is added and the reaction extracted with ethyl acetate. The combined layers are dried with magnesium sulfate and concentrated. The residue is purified by silica gel chromatography using hexane:ethyl acetate (1:3) as eluant. The solid obtained is recrystalized from chloroform:hexane to give the title compound (46.3 mg,):

^{1}H NMR ($CDCl_3$) δ 8.54 (m, 2H), 7.95 (m, 2H), 7.80 (s, 1H), 7.72 (m, 1H), 7.45 (m, 5H), 6.95 (d, 1H, J = 8.6 Hz), 5.33 (s, 2H), 4.53 (m, 1H), 3.96 (s, 3H), 3.72(m, 2H),

3.04 (m 2H), 2.69 (m, 4H), 2.50 (m, 1H), 1.41 (d, 3H, J = 6.3 Hz), 1.01 (d, 3H, J = 6.3 Hz);
^{13}C NMR ($CDCl_3$) δ 164.6, 162.0, 159.3, 154.1, 152.8, 138.6, 134.5, 133.1, 132.2, 130.0, 129.6, 128.8, 128.3, 128.2, 124.9, 124.8, 116.3, 130.0, 129.6, 128.8, 128.3, 128.2, 124.9, 124.8, 116.3, 112.0, 56.3, 55.4, 54.0, 53.0, 52.6, 51.8, 32.3, 16.6, 11.0;
High resolution FAB MS *m/z* found 532.2371 (MH^+), $C_{29}H_{34}N_5O_3S$ requires 532.2382;
Anal. calcd. $C_{29}H_{33}N_5O_3S \cdot H_2O$, C 63.37%, H 6.42%, N 12.74%. Found C 63.05%, H 6.14%, N 12.52%.

Example 18

2-Methoxy-5-[2-[4-(2-phenyl-quinazolin-4-ylamino)-cyclohexyl-amino]-ethyl]-benzenesulfonamide bistrifluoroacetate

4-chloro-2-phenyl quinazoline (0.1185 g, 0.49 mmol) is added to a stirred solution of 5-[2-(4-amino-cyclohexylamino)-ethyl]-2-methoxy-benzenesulfonamide (0.1612 g, 0.49 mmol), prepared as in Intermediate 15, and triethylamine (0.2 ml, 0.98 mmol) in ethanol (5 ml) in a sealed tube and the solution heated to 150°C over 16 h. Saturated sodium carbonate is added and the reaction extracted with ethyl acetate. The combined layers are dried with magnesium sulfate and concentrated. The residue is purified by silica gel chromatography using methanol:ethyl acetate (1:3) containing 1% ammonium hydroxide as eluant, followed by reverse phase HPLC using acetonitrile:water (5% to 40% gradient over 30 min) as eluant to give the title compound (36.7 mg): RP HPLC 21.7 min.;
^{1}H NMR (CD_3OD) δ 8.26-8.23 (m, 2H), 7.98-7.95 (d, 1H, J = 8.3 Hz), 7.63-7.59 (m, 2H), 7.52-7.47 (m, 1H), 7.28-7.14 (m, 5H), 6.85-6.82 (d, 1H, J = 8.6 Hz), 4.27 (br s, 1H), 3.71 (s, 3H), 2.55-2.51 (m, 5H), 1.78-1.72 (m, 2H), 1.58-1.50 (m, 6H);
Anal. Calcd. for $C_{33}H_{35}N_5O_7SF_6$, C 52.17%, H 4.64%, N 9.22%. Found C 52.07%, H 4.70%, N 9.33%;
High resolution FAB MS *m/z* found 532.2389 (MH^+). $C_{29}H_{34}N_5O_3S$ requires 532.2382.

Example 19

(R)-2-methoxy-5-{2-[3-(2-phenyl-quinazolin-4-ylamino)-pyrrolidin-1-yl]-ethyl}-benzenesulfonamide

Synthesized in a manner similar to Example 18, using (R)-5-[2-(3-Amino-pyrrolidin-1-yl)-ethyl]-2-methoxy-benzenesulfonamide (0.50 g, 1.68 mmol), prepared as in Intermediate 16, to give the title compound (322.1 mg):

^{1}H NMR (CD_3OD) δ 8.34-8.30 (m, 2H), 8.03-8.01 (d, 1H, J = 8.0 Hz), 7.73-7.61 (m, 3H), 7.38-7.28 (m, 5H), 6.97-6.95 (d, 1H, J = 8.5 Hz), 4.94-4.88 (m, 1H), 4.78-3.82 (s, 3H), 3.24-3.20 (m, 1H), 3.04-2.99 (m, 1H), 2.80-2.57 (m, 6H), 2.39-2.36 (m, 1H), 1.89-1.86 (m, 1H);

^{13}C NMR (CD_3OD) δ 162.3, 161.2, 156.4, 151.3, 139.6, 134.8, 133.4, 132.6, 131.9, 130.7, 128.9, 128.7, 128.5, 127.7, 126.2, 122.8, 115.2, 113.0, 60.8, 58.3, 56.0, 53.5, 50.9, 34.1, 31.6;

Reverse Phase HPLC (5% to 40% acetonitrile:water) 17.7 min.;

Anal. Calcd. for $C_{27}H_{29}N_5O_3S \cdot H_2O$, C 62.17%, H 5.99%, N 13.43%. Found C 62.43%, H 5.88%, N 13.46%;

High resolution FAB MS *m/z* found 504.2056, $C_{27}H_{30}N_5O_3S$ requires 504.2069.

Example 20

(R)-2-methoxy-5-{2-[1-(2-phenyl-quinazolin-4-yl)-pyrrolidin-3-ylamino]-ethyl}-benzenesulfonamide bistrifluoroacetate

5-(2-Chloro-ethyl)-2-methoxy-benzenesulfonamide (1.29 g, 5.16 mmol) is added to a stirred solution (R)-1-(2-phenyl-quinazolin-4-yl)-pyrrolidin-3-ylamine (1.50 g, 5.16 mmol), prepared as in Intermediate 17, potassium carbonate (1.43 g, 10.32 mmol), and sodium iodide (0.08 g, 0.52 mmol) in ethanol (20 ml) in a sealed tube and the solution heated to 150°C for 16 h. Saturated sodium carbonate is added and the reaction extracted with ethyl acetate. The combined layers are dried with magnesium sulfate and concentrated. The residue is purified by silica gel

chromatography using methanol:ethyl acetate (1:49) containing 1% ammonium hydroxide as eluant, followed by reverse phase HPLC using acetonitrile:water (5% to 40% gradient over 30 min.) as eluant to give (the title compound (15.9 mg):
RP HPLC 18.1 min.;
^{1}H NMR (CD_3OD) δ 8.51-8.49 (d, 1H, *J* = 8.3 Hz), 8.36-8.33 (m, 2H), 8.10-8.00 (m, 2H), 7.82-7.64 (m, 5H), 7.55-7.51 (dd, 1H, *J* = 8.5, 2.4 Hz), 7.19-7.17 (d, 1H, *J* = 8.6 Hz), 4.63-4.54 (m, 3H), 4.45-4.43 (m, 1H), 4.23-4.20 (m, 1H), 3.97 (s, 3H), 3.48-3.41 (m, 2H), 3.08-3.03 (m, 2H), 2.70-2.65 (m, 1H), 2.56-2.51 (m, 1H);
FAB MS *m/z* found 504 (MH^+);
Anal. calcd. for $C_{31}H_{31}N_5O_7SF_6$, C 50.89%, H 4.27%, N 9.57%. Found C 50.46%, H 4.27%, N 9.56%.

Example 21

(S)-2-Methoxy-5-{2-[3-(2-phenyl-quinazolin-4-ylamino)-pyrrolidin-1-yl]-ethyl}-benzenesulfonamide bistrifluoroacetate

4-Chloro-2-phenyl quinazoline (142.4 mg, 0.59 mmol) is added to a stirred solution of (S)-5-[2-(3-Amino-pyrrolidin-1-yl)-ethyl]-2-methoxy-benzenesulfonamide (177.2 mg, 0.59 mmol), prepared as in Intermediate 18, and triethylamine (0.2 ml, 1.18 mmol) in tetrahydrofuran (6 ml) and the solution heated to reflux for 16 h. The solution is concentrated, saturated sodium carbonate added, and the reaction extracted with ethyl acetate. The combined layers are dried with magnesium sulfate and concentrated. The residue is purified by silica gel chromatography using methanol:ethyl acetate (gradient of 1:49 to 1:1) containing 1% ammonium hydroxide as eluant, followed by reverse phase HPLC using acetonitrile:water (5% to 40% gradient over 30 min.) as eluant to give the title compound (120.2 mg):
RP HPLC 18.6 min.;
^{1}H NMR ($CDCl_3$) δ 8.53-8.50 (m, 2H), 7.89-7.85 (m, 2H), 7.70-7.65 (m, 2H), 7.47-7.34 (m, 4H), 7.27-7.20 (m, 1H), 6.83-6.80 (d, 1H, *J* = 8.3 Hz), 6.46-6.44 (d, 1H, *J* = 7.3 Hz), 5.90-5.30 (br s, 2H), 5.02 (m, 1H), 3.84 (s, 3H), 2.92-2.82 (m, 2H), 2.72-2.28 (m, 7H), 1.84-1.81 (m, 1H);

^{13}C NMR (CD_3OD) δ 162.0, 160.9, 156.2, 151.1, 140.0, 135.3, 133.9, 132.8, 131.7, 131.3, 129.5, 129.3, 129.0, 128.2, 126.7, 123.3, 115.0, 113.5, 61.2, 58.7, 56.7, 54.0, 51.4, 34.6, 32.1; Anal. Calcd. for $C_{31}H_{31}F_6N_5O_7S \cdot H_2O$, C 49.67%, H 4.44%, N 9.34%. Found C 49.67%, H 4.23%, N 9.23%;
High resolution FAB MS *m/z* found 504.2064 (MH^+), $C_{27}H_{30}N_5O_3S$ requires 504.2069.

Example 22

(S)-N-Acetyl-2-methoxy-5-{2-[3-(2-phenyl-quinazolin-4-ylamino)-pyrrolidin-1-yl]-ethyl}-benzenesulfonamide bistrifluoroacetate

(S)-2-Methoxy-5-{2-[3-(2-phenyl-quinazolin-4-ylamino)-pyrrolidin-1-yl]-ethyl}-benzenesulfonamide bistrifluoroacetate, prepared as in Example 21, is added to a stirring solution of acetic anhydride (5.9 mg, 57.9 mmol), diisopropyl ethyl amine (5.0 µl, 28.9 µmol), and N,N-dimethyl amino pyridine (catalytic 0.1%) in tetrahydrofuran (10 ml) and the solution heated to reflux 16 h. The solution is concentrated and the residue purified by reverse phase HPLC using acetonitrile:water (20% to 30% gradient over 30 mIn.) as eluant to give the title compound (4.5 mg):
RP HPLC 10.1 min.;
High resolution FAB MS *m/z* found 546.2181 (MH^+), $C_{29}H_{32}N_5O_4S$ requires 546.2175.

Example 23

(S)-2-Hydroxy-5-{2-[3-(2-phenyl-quinazolin-4-ylmino)-pyrrolidin-1-yl]-ethyl}-benzenesulfonamide bistrifluoroacetate

Boron tribromide (1M solution in dichloromethane, 0.2 ml, 202.0 mmol) is added to a stirred solution of (S)-N-Acetyl-2-methoxy-5-{2-[3-(2-phenyl-quinazolin-4-ylamino)-pyrrolidin-1-yl]-ethyl}-benzenesulfonamide bistrifluoroacetate, prepared as in Example 22, in dichloromethane at 0°C. The solution is allowed to warm to room temperature over 2 h. Methanol is added (5 ml), the solution stirred for 10 min. , and

then concentrated. The residue is taken up in aqueous methanol (50%, 10 ml) and the solution stirred for 10 mins. Aqueous sodium bicarbonate (5%, 10 ml) is added and the reaction extracted with ethyl acetate. The combined layers are dried with sodium sulfate and concentrated. The residue is purified by reverse phase HPLC using acetonitrile:water (10% to 25% gradient over 30 mins.) as eluant to give the title compound (8.1 mg):

RP HPLC 20.6 min.,

^{1}H NMR (CD_3OD) δ 8.37-8.35 (m, 2H), 8.01 (m, 2H), 7.75-7.68 (m, 6H), 7.39-7.36 (m, 1H), 6.97-6.94 (d, 1H, J = 8.3 Hz), 5.42-5.31 (m, 1H), 4.02-3.79 (m, 3H), 3.53 (m, 4H), 3.07 (m, 4H);

High resolution FAB MS *m/z* found 490.1912 (MH^+), $C_{26}H_{28}N_5O_3S$ requires 490.1913.

Example 24

(S)-2-methoxy-5-[2-[1-(2-phenyl-quinazolin-4-yl)-pyrrolidin-3-ylamino]-ethyl]-benzenesulfonamide bistrifluoroacetate

Synthesized in a manner similar to Example 20, using 5-(2-Chloro-ethyl)-2-methoxy-benzenesulfonamide (1.72 g, 6.89 mmol) and (S)-1-(2-phenyl-quinazolin-4-yl)-pyrrolidin-3-ylamine (2.0 g, 6.89 mmol), prepared as in Intermediate 19, to give the title compound (78.8 mg):

RP HPLC 18.2 mins.;

^{1}H NMR (CD_3OD) δ 8.41-8.38 (m, 1H), 8.25-8.23 (m, 2H), 7.97-7.90 (m, 2H), 7.70-7.54 (m, 5H), 7.44-7.41 (m, 1H), 7.09-7.06 (m, 1H), 4.53-4.41 (m, 3H), 4.35-4.33 (m, 1H), 4.13-4.10 (m, 1H), 3.87 (s, 3H), 3.38-3.32 (m, 2H), 2.98-2.93 (m, 2H), 2.60-2.56 (m, 1H), 2.46-2.42 (m, 1H);

Anal. Calcd. for $C_{27}H_{29}N_5O_3S$, C 50.89%, H 4.27%, N 9.57%. Found C 50.43%, H 4.28%, N 9.47%;

High resolution FAB MS *m/z* found 504.2060 (MH^+), $C_{27}H_{30}N_5O_3S$ requires 504.2069.

Example 25

2-Methoxy-5-{2-[5-(2-phenyl-quinazolin-4-yl)-2,5-diazo-bicyclo[2.2.1]hept-2-yl]-ethyl}-benzenesulfonamide bistrifluoroacetate

Synthesized in a manner similar to Example 20, using 5-(2-Chloro-ethyl)-2-methoxy-benzenesulfonamide (0.14 g, 0.56 mmol) and 4-(2,5-diaza-bicyclo[2.2.1]hept-2-yl)-2-phenyl-quinazoline (0.17 g, 0.56 mmol), prepared as in Intermediate 20, to give the title compound (75.7 mg):
RP HPLC 17.4 mins.;
^{1}H NMR (CD_3OD) δ 8.30-8.27 (m, 2H), 8.03-8.01 (d, 1H, J = 8.0 Hz), 7.73-7.56 (m, 3H), 7.39-7.24 (m, 5H), 6.94-6.91 (m, 1H), 5.18 (m, 1H), 3.90 (m, 1H), 3.79 (s, 3H), 3.68 (m, 1H), 3.22-3.21 (m, 2H), 2.98 (m, 2H), 2.69-2.64 (m, 4H);
Anal. calcd. for $C_{32}H_{31}N_5O_7SF_6$, C 51.68%, H 4.20%, N 9.42%. Found C 52.46%, H 4.40%, N 9.78%;
High resolution FAB MS *m/z* found 516.2070 (MH^+), $C_{28}H_{30}N_5O_3S$ requires 516.2069.

Example 26

2-Methoxy-5-(2-{methyl-[2-(2-phenyl-quinazolin-4-ylamino)-ethyl]-amino}-ethyl)-benzenesulfonamide bistrifluoroacetate

Synthesized in a manner similar to Example 20, using 5-(2-Chloro-ethyl)-2-methoxy-benzenesulfonamide (1.81 g, 7.24 mmol) and N-methyl-N-(2-phenyl-quinazolin-4-yl)-ethane-1,2-diamine (2.00 g, 7.24 mmol), prepared as in Intermediate 21, to give the title compound (5.3 mg):
RP HPLC 16.6 min.;
^{1}H NMR (CD_3OD) δ 8.32-8.29 (m, 2H), 7.88-7.85 (m, 1H), 7.71-7.59 (m, 3H), 7.40-7.35 (m, 4H), 7.25-7.24 (m, 1H), 6.85-6.83 (m, 1H), 3.99-3.77 (m, 5H), 2.80-2.68 (m, 6H), 2.67 (s, 3H);
Anal. calcd. for $C_{30}H_{37}N_5O_{10}SF_6$, C 47.68%, H 4.67%, N 9.27%. Found C 48.09%, H 4.28%, N 9.14%;

High resolution FAB MS *m/z* found 492.2071 (MH^+), $C_{26}H_{30}N_5O_3S$ requires 492.2069.

Example 27

2-Methoxy-5-{2-{methyl-[2-(2-phenyl-quinazoline-4-sulfinyl)-ethyl]-amino}-ethyl)-benzenesulfonamide

4-Chloro-2-phenyl quinazoline (0.17 g, 0.72 mmol) is added to a stirred solution of 5-{2-[(2-Mercapto-ethyl)-methyl-amino]-ethyl}-2-methoxy-benzenesulfonamide (0.22 g, 0.72 mmol), prepared as in Intermediate 22, and sodium hydride (60% suspension, 0.03 g, 0.86 mmol) in 1,4-dioxane and the solution heated to reflux for 16 h. The reaction is quenched with water:1,4-dioxane (1:1). Saturated sodium carbonate is added and the reaction extracted with ethyl acetate. The combined layers are dried with magnesium sulfate and concentrated. The residue is purified by silica gel chromatography using methanol:ethyl acetate (1:9) as eluant to give the title compound (1.4 mg):
Reverse phase HPLC analysis 22.9 min. using acetonitrile:water (5% to 40% gradient over 30 mins.),
^1H NMR ($CDCl_3$) δ 8.42-8.39 (m, 2H), 8.09-8.06 (d, 1H, J = 8.6 Hz), 7.99-7.96 (d, 1H, J = 8.5 Hz), 7.77-7.72 (t, 1H, J = 8.3 Hz), 7.62 (s, 1H), 7.47-7.40 (m, 4H), 7.32-7.30 (d, 1H, J = 8.3 Hz), 6.81-6.78 (d, 1H, J = 8.6 Hz), 5.23 (s, 2H), 4.42-4.19 (m, 2H), 3.88 (s, 3H), 3.59 (s, 3H), 3.41-3.10 (m, 2H), 3.07-2.85 (m, 4H);
High resolution FAB MS *m/z* found 525.1632 (MH^+), $C_{26}H_{29}N_4O_4S_2$ requires 525.1630.

Example 28

2-Methoxy-5-{2-[3-(2-phenyl-quinazolin-4-yloxy)-pyrrolidin-1-yl]-ethyl}-benzenesulfonamide

Synthesized in a manner similar to Example 20, using 5-(2-Chloro-ethyl)-2-methoxy-benzenesulfonamide (0.86 g, 3.43 mmol) and 2-Phenyl-4-(pyrrolidin-3-

yloxy)-quinazoline (1.00 g, 3.43 mmol), prepared as in Intermediate 23, to give the title compound (0.23 g):
Reverse phase HPLC analysis 22.9 min. using acetonitrile:water (5% to 40% gradient over 30 mins.),
^{1}H NMR ($CDCl_3$) δ 8.57-8.54 (m, 2H), 8.19-8.16 (m, 1H), 7.99-7.96 (d, 1H, *J* = 8.3 Hz), 7.83-7.78 (m, 1H), 7.74-7.73 (m, 1H), 7.53-7.49 (m, 4H), 7.35-7.32 (dd, 1H, *J* = 8.5, 2.2 Hz), 6.90-6.87 (d, 1H, *J* = 8.5 Hz), 5.85-5.84 (m, 1H), 5.39 (br s, 2H), 3.90 (s, 3H), 3.09-2.92 (m, 3H), 2.83-2.57 (m, 6H), 2.18 (m, 1H);
Anal. calcd. for $C_{27}H_{28}N_4O_4S$, C 64.27%, H 5.59%, N 11.10%. Found C 64.19%, H 5.57%, N 11.05%;
High resolution FAB MS *m/z* found 505.1906, $C_{27}H_{29}N_4O_4S$ requires 505.1910.

Example 29

(2S,4S)-2-Methoxy-5-{2-[2-methyl-4-(2-phenyl-quinazolin-4-ylamino)-pyrrolidin-1-yl]-ethyl}-benzenesulfonamide bistrifluoroacetate

5-(2-Chloro-ethyl)-2-methoxy-benzenesulfonamide (0.07 g, 0.296 mmol) is added to a stirred solution of (2S, 4S)-(2-Methyl-pyrrolidin-4-yl)-(2-phenyl-quinazolin-4-yl)-amine (0.09 g, 0.296 mmol), prepared as in Intermediate 24, sodium carbonate (0.08 g, 0.592 mmol), and sodium iodide (0.09 g, 0.592 mmol) in ethanol (6 ml) and the solution heated to 150°C in a sealed tube. After 24 hrs., more 5-(2-Chloro-ethyl)-2-methoxy-benzenesulfonamide (0.06 g, 0.24 mmol) is added, because the reaction is not complete by TLC using methanol:ethyl acetate (1:9) containing 1% ammonium hydroxide as eluant. After another 48 h., saturated sodium carbonate is added and the reaction extracted with ethyl acetate. The combined layers are dried with sodium sulfate and concentrated. The residue is purified by silica gel chromatography using methanol:ethyl acetate (1:9) containing 1% ammonium hydroxide as eluant, followed by reverse phase HPLC using acetonitrile:water (5% to 40% gradient over 30 mins.) to give the title compound (62.0 mg):
RP HPLC 19.1 mins.;
^{1}H NMR ($CDCl_3$) δ 8.55-8.52 (m, 2H), 7.90-7.84 (m, 1H), 7.70-7.69 (m, 2H), 7.46-7.31 (m, 6H), 6.90-6.87 (d, 1H, *J* = 8.6 Hz), 6.14-6.08 (m, 1H), 5.53-5.28 (m, 2H),

5.03-4.91 (m, 1H), 3.89-3.75 (m, 6H), 3.09-2.88 (m, 1H), 2.73-2.68 (m, 4H), 2.40-2.21 (m, 2H), 1.11-1.09 (d, 3H), J = 5.8 Hz);
Anal. Calcd. for $C_{32}H_{33}N_5O_7SF_6$, C 51.54%, H 4.46 %, N 9.39%. Found C 51.26%, H 4.64%, N 9.20%;
High resolution FAB MS *m/z* found 518.2222 (MH^+), $C_{28}H_{32}N_5O_3S$ requires 518.2226.

Example 30

(2R,4S)-2-Methoxy-5-{2-[2-methyl-4-(2-phenyl-quinazolin-4-ylamino)-pyrrolidin-1-yl]-ethyl}-benzenesulfonamide bistrifluoroacetate

5-(2-Chloro-ethyl)-2-methoxy-benzenesulfonamide (0.07 g, 0.288 mmol) is added to a stirred solution of (2R, 4S)-(2-Methyl-pyrrolidin-4-yl)-(2-phenyl-quinazolin-4-yl)-amine (0.09, 0.288 mmol), prepared as in Intermediate 25, sodium carbonate (0.08 g, 0.576 mmol), and sodium iodide (0.09 g, 0.576 mmol) in 1,4-dioxane (10 ml) and the solution set to reflux for 16 h. More 5-(2-Chloro-ethyl)-2-methoxy-benzenesulfonamide (0.07 g, 0.288 mmol) is added and continued to reflux 16 h. The solution is then transfered to a sealed tube and heated to 150°C for 16 h. due to the slow reaction time. Saturated sodium carbonate is added and the reaction is extracted with ethyl acetate. The combined layers are dried with sodium sulfate and concentrated. The residue is purified by silica gel chromatography using methanol:ethyl acetate (1:9) containing 1% ammonium hydroxide as eluant, followed by reverse phase HPLC using acetonitrile:water (5% to 40% gradient over 30 mins.) to give the title compound (3.5 mg):
RP HPLC 20.6 min.;
^1H NMR (CD_3OD) δ 8.54-8.52 (d, 1H, J = 8.3 Hz), 8.37-8.34 (m, 2H), 8.08-7.99 (m, 2H), 7.82-7.67 (m, 5H), 7.55-7.51 (dd, 1H, J = 8.5, 2.2 Hz), 7.17-714 (d, 1H, J = 8.5 Hz), 5.47 (m, 1H), 3.99-3.93 (m, 6H), 3.71 (m, 2H), 3.12-2.99 (m, 3H), 2.33-2.19 (m, 1H), 1.61-1.59 (d, 3H, J = 6.4 Hz);
High resolution FAB MS *m/z* found 518.2222 (MH^+), $C_{28}H_{32}N_5O_3S$ requires 518.2226.

Example 31

(3S,4R)-2-Methoxy-5-{2-[3-methyl-4-(2-phenyl-quinazolin-4-ylamino)-pyrrolidin-1-yl]-ethyl}-benzenesulfonamide bistrifluoroacetate

5-(2-Chloro-ethyl)-2-methoxy-benzenesulfonamide (0.57 g, 2.27 mmol) is added to a stirred solution of (3S, 4R)-(4-Methyl-pyrrolidin-3-yl)-(2-phenyl-quinazolin-4-yl)-amine (0.46, 1.50 mmol), prepared as in Intermediate 26, sodium carbonate (0.41 g, 3.00 mmol), and sodium iodide (0.45 g, 3.00 mmol) in ethanol (15 ml) and the solution set to reflux at 150°C for 48 h. Saturated sodium carbonate is added and the reaction extracted with ethyl acetate. The combined layers are dried with sodium sulfate and concentrated. The residue is purified by silica gel chromatography using methanol:ethyl acetate (1:9) containing 1% ammonium hydroxide as eluant, followed by reverse phase HPLC using acetonitrile:water (5% to 40% gradient over 30 mins.) as eluant to give the title compound (232.6 mg):
RP HPLC 19.7 mins.;
^{1}H NMR (CD_3OD) δ 8.57-8.55 (d, 1H, *J* = 8.3 Hz), 8.38-8.36 (d, 2H, *J* = 7.5 Hz), 8.11-8.07 (t, 1H, *J* = 7.6 Hz), 8.03-8.01 (d, 1H, *J* = 8.2 Hz), 7.83-7.75 (m, 3H), 7.70-7.67 (t, 2H, *J* = 7.6 Hz), 7.53-7.51 (dd, 1H, *J* = 8.4, 2.2 Hz), 7.16-7.14 (d, 1H, *J* = 8.5 Hz), 5.22-5.20 (m, 1H), 3.96-3.94 (m, 6H), 3.56-3.52 (m, 2H), 3.11-3.07 (m, 3H), 2.97-2.82 (m, 1H), 1.35-1.34 (d, 3H, *J* = 6.5 Hz);
Anal. calcd. for $C_{32}H_{33}N_5O_7SF_6$, C 51.54%, H 4.46%, N 9.39%. Found C 51.26%, H 4.52%, N 9.42%;
High resolution FAB MS *m/z* found 518.2217 (MH^+), $C_{28}H_{32}N_5O_3S$ requires 518.2226.
The racemic compound is separated into its enantiomers by normal phase HPLC with a Chiralpak AD (2 cm x 25 cm) column using hexane:isopropyl alcohol (85:15) containing 1% diethyl amine at 254 nm to obtain (3S,4R)-2-Methoxy-5-{2-[3-methyl-4-(2-phenyl-quinazolin-4-ylamino)-pyrrolidin-1-yl]-ethyl}-benzenesulfonamide bistrifluoroacetate (NP HPLC 39.0 mins.) and (3S,4R)-2-Methoxy-5-{2-[3-methyl-4-(2-phenyl-quinazolin-4-ylamino)-pyrrolidin-1-yl]-ethyl}-benzenesulfonamide bistrifluoroacetate(NP HPLC 46.0 mins.).

Example 32

2-Benzyl-4-{2-[4-(2-phenylquinazolin-4-yl)piperazin-1-yl]ethyl}phenol

2-Benzyl-4-(2-bromoethyl)phenol (0.20 g, 0.70 mmole), prepared as in Intermediate 27, and 4-(piperazin-1-yl)-2-phenyl-quinazoline (0.17 g, 0.58 mmole) are dissolved in acetonitrile (5 mL). Diisopropylethyl amine (0.60 mL, 3.44 mmole) is added and the mixture is heated to 80°C for 4 hours. The mixture is allowed to cool to 23°C and water (20 mL) is added. The mixture is extracted with ethyl acetate (3 x 5 mL). The combined organics are dried ($MgSO_4$) and concentrated in vacuo. The residue is chromatographed on silica gel and eluted with 50:50 hexanes:ethyl acetate to afford 2-benzyl-4-{2-[4-(2-phenylquinazolin-4-yl)piperazin-1-yl]ethyl}phenol as a light yellow solid (0.11 g).

^1H NMR ($CDCl_3$) δ 8.58 (d, 2H), 7.98 (d, 1H), 7.89 (d, 1H), 7.70 (t, 1H), 7.50-7.38 (m, 4H), 7.31-7.18 (m, 6H), 6.99 (br s, 2H), 6.70 (d, 1H), 3.98 (s, 2H), 3.90 (br s, 4H), 2.79 (br s, 6H), 2.62 (m, 2H) ppm.

FABMS for $C_{33}H_{32}N_4O$: calcd; 500.28. Found; 501.3 (MH^+).

Anal calcd for $C_{33}H_{32}N_4O \cdot 0.67\ H_2O$: C, 77.3%; H, 6.6%; N, 10.9%. Found: C, 77.23%; H, 6.64%; N, 10.48%.

Example 33

N-(2-Hydroxy-5-{2-[4-(2-phenylquinazolin-4-yl)piperazin-1-yl]ethyl}phenyl)acetamide

3-(N-Acetyl)amino-4-methoxyphenethyl p-toluenesulfonate (0.26 g, 0.72 mmole), prepared as in Intermediate 28, and 4-piperazin-1-yl-2-phenyl-quinazoline (0.17 g, 0.60 mmole) are dissolved in acetonitrile (5 mL). Potassium iodide (0.30 g, 1.83 mmole) is added, followed by diisopropyl ethyl amine (0.37 mL, 2.12 mmole). The solution is heated to 85°C for 18 hours. Water (15 mL) is added and the mixture is extracted with ethyl acetate (3 x 5 mL). The combined organics are dried ($MgSO_4$) and concentrated in vacuo. The residue is chromatographed on silica gel and eluted with 10:63:27 isopropanol:ethyl acetate:hexanes to afford N-(2-Hydroxy-

5-{2-[4-(2-phenylquinazolin-4-yl)piperazin-1-yl]ethyl}phenyl)acetamide (0.204 g) as a light yellow solid.
^{1}H NMR ($CDCl_3$) δ 8.57 (d, 2H), 8.29 (s, 1H), 7.96 (d, 1H), 7.90 (d, 1H), 7.72 (m, 2H), 7.50-7.38 (m, 4H), 6.89 (d, 1H), 6.79 (d, 1H), 3.91 (m, 4H), 3.84 (s, 3H), 2.82-2.65 (m, 8H), 2.19 (s, 3H) ppm.
FABMS for $C_{29}H_{31}N_5O_2$: calcd; 481.3. Found; 481.89.
Anal. calcd. for $C_{29}H_{31}N_5O_2 \cdot 0.5\ H_2O$: C, 70.98%; H, 6.58%; N, 14.3%. Found: C, 70.79%; H, 6.60%; N, 14.06%.

Example 34

1-(2-Methoxy-5-{2-[4-(2-phenylquinazolin-4-yl)piperazin-1-yl]ethyl}phenyl]ethanone

Synthesized in a manner similar to Example 33, using Toluene-4-sulfonic acid 2-(3-acetyl-4-methoxyphenyl)ethyl ester (0.59 g, 1.69 mmole), prepared as in Intermediate 29, and 4-(piperazin-1-yl)-2-phenyl-quinazoline (0.34 g, 1.18 mmole) to afford the title compound (0.32 g) as a light yellow solid.
^{1}H NMR ($CDCl_3$) δ 8.59 (d, 2H), 7.99 (d, 1H), 7.91 (d, 1H), 7.75 (m, 1H), 7.61 (s, 1H), 7.51-7.33 (m, 6H), 6.90 (d, 1H), 3.91 (br s, 7H), 2.84-2.61 (m, 6H), 2.61 (s, 3H) ppm.
FABMS for $C_{29}H_{30}N_4O_2$: calcd, 466.25. Found, 467.2 (MH^+).
Anal calcd. for $C_{29}H_{30}N_4O_2 \cdot 0.25\ H_2O$: C, 73.9%; H, 6.5%; N, 11.9%. Found: C, 73.80%; H, 6.61%; N, 11.62%.

Example 35

1-{6-[4-(2-Phenylquinazolin-4-yl)piperazin-1-yl]hexanoyl}pyrrolidin-2-one

Synthesized in a manner similar to Example 33, using 1-(6-Bromohexanoyl)-2-pyrrolidinone (0.91 g, 3.43 mmole), prepared as in Intermediate 30, and 4-(piperazin-1-yl)-2-phenyl-quinazoline (0.50 g, 1.73 mmole) to yield the title compound (0.45 g) as a white solid.

^{1}H NMR (CD_3OD) δ 8.47 (d, 2H), 8.16 (d, 1H), 8.02 (d, 1H), 7.97 (m, 1H), 7.63 (m, 1H), 7.58 (m, 3H), 6.25 (s, 4H), 3.79 (t, 2H), 3.59 (br s, 4H), 3.37 (br s, 4H), 3.25 (m, 2H), 2.96 (t, 2H), 2.59 (t, 2H), 2.02 (m, 2H), 1.83 (m, 2H), 1.72 (m, 2H), 1.49 (m, 2H) ppm.

FABMS for $C_{28}H_{33}N_5O_2$: calcd, 471.3. Found: 472.1 (MH^+).

Anal. calcd. for $C_{28}H_{33}N_5O_2$: C, 61.4%; H, 5.9%; N, 10.0%. Found: C, 61.28%; H, 6.04%; N, 9.93%.

Example 36

1-Methanesulfonyl-3-{2-[4-(2-phenylquinazolin-4-yl)piperazin-1-yl]ethyl}imidazolidin-2-one bismaleate

Synthesized in a manner similar to Example 33, using 1-(2-Chloroethyl)-3-methanesulfonyl-2-imidazolidinone (2.23 g, 9.84 mmole), prepared as in Intermediate 31, and 4-(piperazin-1-yl)-2-phenyl-quinazoline (1.44 g, 4.96 mmole) to afford the title compound (0.615 g) as a tan solid.

^{1}H NMR (CD_3OD) δ 8.39 (d, 2H), 8.19 (d, 1H), 7.98 (m, 2H), 7.62 (m, 4H), 6.26 (s, 4H), 4.37 (br s, 4H), 3.89 (t, 2H), 3.60 (m, 4H), 3.29 (br s, 4H), 3.22 (s, 3H), 3.09 (t, 2H) ppm.

FABMS for $C_{24}H_{28}N_6O_3S$: calcd, 480.3. Found: 481.1 (MH^+).

Anal calcd. for $C_{32}H_{36}N_6O_{11}S \cdot 1.0\ H_2O$: C, 52.6%; H, 5.2%; N, 11.5%. Found: C, 52.62%; H, 5.34%; N, 10.89%.

Example 37

1-(2,2-Dimethylpropionyl)3-{2-[4-(2-phenylquinazolin-4-yl)piperazin-1-yl]ethyl}imidazolidin-2-one

1-(2-Chloroethyl)-3-trimethylacetyl-2-imidazolidinone (1.90 g, 8.18 mmole), prepared as in Intermediate 32, is dissolved in 1,4-dioxane (20 mL). 4-(piperazin-1-yl)-2-phenyl-quinazoline (1.22 g, 4.20 mmole) is added. Potassium iodide (1.50 g, 9.04 mmole) is added, followed by diisopropylethyl amine (2.20 mL, 12.6 mmole).

The solution is heated to 90°C for 48 hours. The mixture is cooled to 23°C and water (50 mL) is added. The mixture is extracted with ethyl acetate (4 x 10 mL). The combined organics are dried ($MgSO_4$) and concentrated in vacuo. The residue is chromatographed on silica gel and eluted with a) 70/21/9 isopropanol/ethyl acetate/hexanes; b) 90/10 chloroform/methanol to provide the title compound (0.732 g) as a white solid. ^1H NMR ($CDCl_3$) δ 8.57 (d, 2H), 7.99 (d, 1H), 7.89 (d, 1H), 7.74 (t, 1H), 7.44 (m, 4H), 3.83 (m, 6H), 3.48 (m, 4H), 2.78 (br s, 4H), 2.62 (t, 2H), 1.39 (s, 9H) ppm. FABMS calcd. for $C_{28}H_{34}N_6O_2$: 486.3. Found: 487.2 (MH^+). Anal. calcd. for $C_{28}H_{34}N_6O_2 \cdot 0.33\ H_2O$: C, 6

Example 38

1-{4-[4-(2-Phenylquinazolin-4-yl)piperazin-1-yl]butyryl}piperidin-2-one bis maleate

1-(4-Bromobutyryl)-δ-valerolactam (1.71 g, 6.88 mmole), prepared as in Intermediate 33, is dissolved in 1,4-dioxane (10 mL). 4-(piperazin-1-yl)-2-phenyl-quinazoline (1.02 g, 3.51 mmole) is added, followed by diisopropylethyl amine (1.80 mL, 10.3 mmole). The solution is heated to 90°C for 2 hours. Water (40 mL) is added and the solution is extracted with methylene chloride (3 x 10 mL). The combined organics are dried ($MgSO_4$) and concentrated in vacuo. The residue is chromatographed on silica gel and eluted with 70/21/9 isopropanol/ethyl acetate/hexanes. The residue is dissolved in ethanol (2 mL). Maleic acid (0.31 g, 2 equivalents) is dissolved in ethanol (1 mL) and is added. The solution is allowed to stand at 23°C for 15 minutes, in the refrigerator (at -20°C) for 4 days. The mixture is filtered to yield the title compound (0.408 g) as a white solid.
^1H NMR (CD_3OD) δ 8.44 (d, 2H), 8.17 (d, 1H), 8.00 (m, 1H), 7.97 (t, 1H), 7.63 (t, 1H), 7.58 (m, 3H), 6.24 (s, 4H), 4.26 (br s, 4H), 3.72 (m, 2H), 3.59 (m, 6H), 3.07 (t, 2H), 2.58 (m, 2H), 2.17 (m, 2H), 1.82 (m, 4H) ppm.
FABMS calcd for $C_{27}H_{31}N_5O_2$: 457.3. Found: 458.1 (MH^+).
Anal. calcd. for $C_{35}H_{39}N_5O_{10} \cdot 0.33\ H_2O$: C, 60.4%; H,5.8%; N, 10.1%. Found: C, 60.60%; H, 5.64%; N, 10.02%.

Example 39

5-[2-((3-(S)-((2-Phenyl-quinazolin-4-yl)aminomethyl))-pyrrolidin-1-yl)-ethyl]-2-methoxy-benzenesulfonamide hydrochloride

A solution of crude 5-[2-((3-(R)-(N-phenylmethyl-(2-phenyl-quinazolin-4-yl)aminomethyl))-pyrrolidin-1-yl)-ethyl]-2-methoxy-benzenesulfonamide bistrifluoroacetate (330 mg), prepared as in Intermediate 34, in MeOH (70 mL) and water (20 mL) is heated under reflux for 20h with 10% Pd/C (500 mg) and ammonium formate (2g). The cooled mixture is filtered through celite and evaporated. The residue is treated with water (20 mL) and extracted with EtOAc (3 x 30 mL) and the combined organic layers are dried ($MgSO_4$) and evaporated. The residue is purified by chromatography using EtOAc then 50% MeOH-EtOAc as eluent to afford a brown foam. This is dissolved in methanol, treated with ethereal hydrogen chloride and the resulting solid collected by filtration and dried under vacuum to afford the title compound as a tan solid (85 mg).
mp. 200°C (decomp).
^{1}H NMR (DMSO-d_6) δ 11.36 (br d, 0.5H), 10.73 (br s, 0.5H), 8.76 (t, J = 8.1 Hz, 1H), 8.57 (d, J = 8.1 Hz, 1H), 8.50 (d, J = 8.1 Hz, 1H), 8.30 (d, J = 8.1 Hz, 1H), 8.04 (t, J = 7.6 Hz, 1H), 7.85-7.55 (m, 4H), 7.44 (m, 1H), 7.15 (d, J = 8.4 Hz, 1H), 7.05 (br s , 3H), 3.86 (s, 3H), 4.00-2.80 (m, 11H), 2.40-1.80 (m, 3H).
Anal Found: C, 54.26; H, 6.02; N, 10.44. $C_{28}H_{31}N_5O_3S.2HCl.2H_2O$ Requires: C, 53.67; N, 5.95; N, 11.18%.

Example 40

5-[2-((3-(R)-((2-Phenyl-quinazolin-4-yl)aminomethyl))-pyrrolidin-1-yl)-ethyl]-2-methoxy-benzenesulfonamide trifluoroacetate

Prepared as in Example 39 from 5-[2-((3-(S)-(N-phenylmethyl-(2-phenyl-quinazolin-4-yl)aminomethyl))-pyrrolidin-1-yl)-ethyl]-2-methoxy-benzenesulfonamide bistrifluoroacetate, prepared as in Intermediate 35, except that the desired

compound is purified by reverse phase chromatography to afford the title compound as a tan foam (62 mg).

mp. 118-21°C.

Anal Found: C, 47.79; H, 4.24; N, 8.51. $C_{28}H_{31}N_5O_3S.2.5CF_3CO_2H.1.5H_2O$

Requires: C, 47.77; N, 4.43; N, 8.44%

Example 41

1-(2-Phenyl-1,3-quinazolin-4-yl)-4-[3-(3-indolyl)propyl]-1,4-piperazine

A solution of 3-(3-indolyl)-1-propyl methanesulfonate (1.00 g, 3.95 mmol), prepared as in Intermediate 36, in dioxane (5 mL) is treated with 1-(2-phenyl-1,3-quinazoline-4-yl)-1,4-piperazine (1.38 g, 4.75 mmol) and diisopropylethylamine (2.1 g, 12.2 mmol). The mixture is heated at 100°C for 14 h. The mixture is cooled to 25°C, is diluted with water and is extracted with ethyl acetate. The combined organics are washed with water, brine, are dried over magnesium sulfate, and are concentrated in vacuo. The crude product is chromatographed on 80 g of silica gel (elution with 30% ethyl acetate - hexane followed by 50% ethyl acetate:hexane followed by 70% ethyl acetate:hexane followed by ethyl acetate) to give 1-(2-phenyl-1,3-quinazolin-4-yl)-4-[3-(3-indolyl)propyl]-1,4-piperazine (950 mg) as an amorphous solid.

^1H NMR ($CDCl_3$) δ 8.61 (d, J = 6 Hz, 2H, ArH), 8.02 (bs, 1H, NH), 8.00 (d, J = 8 Hz, 1H, ArH), 7.90 (d, J = 8 Hz, 1H, ArH), 7.72 (t, J = 7 Hz, 1H, ArH), 7.64 (d, J = 8 Hz, 1H, ArH), 7.45 (bs, 2H, ArH), 7.42 (t, J = 7 Hz, 1H, ArH), 7.38 (t, J = 7 Hz, 1H, ArH), 7.20 (m, 3H, ArH), 7.01 (s, 1H, ArH), 3.94 (bs, 4H, CH_2N), 2.86 (t, J = 7 Hz, 2H, $ArCH_2$), 2.64 (bs, 4H, CH_2N), 2.58 (t, 2H, J = 8 Hz, CH_2N), 2.02 (m, 2H, CH_2) ppm.

Anal. Calcd for $C_{29}H_{29}N_5$: C, 77.82; H, 6.53; N, 15.65. Found: C, 77.64; H, 6.69; N, 15.43.

Example 42

1-(2-Phenyl-1,3-quinazolin-4-yl)-4-[2-(3-hydroxymethyl-4-methoxyphenyl)ethyl]-1,4-piperazine

A solution of crude 2-(3-hydroxymethyl-4-methoxyphenyl)ethylmethanesulfonate (2.0 g), prepared as in Intermediate 37, in dioxane (10 mL) is treated with 1-(2-phenyl-1,3-quinazoline-4-yl)-1,4-piperazine (1.50 g, 5.17 mmol) and diisopropylethylamine (3.0 mL, 17.5 mmol). The mixture is heated at 90°C for 10 h, then is diluted with water and extracted with ethyl acetate. The organics are dried over magnesium sulfate and are concentrated in vacuo. The crude product is chromatographed on 40 g of silica gel (elution with 40% ethyl acetate - hexane followed by 70% ethyl acetate:hexane followed by 20% isopropanol in 70% ethyl acetate:hexane) to afford the title compound (510 mg) as an amorphous solid.

^{1}H NMR ($CDCl_3$) δ 8.56 (d, J = 8 Hz, 2H, ArH), 7.98 (d, J = 8 Hz, 1H, ArH), 7.88 (d, J = 8 Hz, 1H, ArH), 7.71 (t, J = 7 Hz, 1H, ArH), 7.45 (m, 3H, ArH), 7.40 (t, J = 7 Hz, 1H, ArH), 7.15 (s, 1H, ArH), 7.14 (d, J = 8 Hz, 1H, ArH), 6.81 (d, J = 8 Hz, 1H, ArH), 4.66 (s, 2H, $ArCH_2O$), 3.94 (bs, 4H, CH_2N), 3.84 (s, 3H, CH_3O), 2.80 (m, 2H, $ArCH_2$), 2.78 (bs, 4H, CH_2N), 2.64 (m, 2H, CH_2N) ppm.

Anal. Calcd for $C_{28}H_{30}N_4O_2$: C, 73.98; H, 6.65; N, 12.33. Found: C, 73.76; H, 6.61; N, 12.20.

Example 43

1-(2-Phenyl-1,3-quinazolin-4-yl)-4-[2-(3-methanesulfonylaminomethyl-4-methoxyphenyl)ethyl]-1,4-piperazinetrifluoroacetate

A solution of 2-(3-methanesulfonylaminomethyl-4-methoxyphenyl)ethyl-p-toulenesulfonate (390 mg, 0.986 mmol), prepared as in Intermediate 38, in dioxane (4 mL) is treated with 1-(2-phenyl-1,3-quinazolin-4-yl)-1,4-piperazine (286 mg, 0.985 mmol) and diisopropylethylamine (0.52 mL, 3.03 mmol). The mixture is heated at 90°C for 12 h, then is cooled to 25°C and is diluted with water. The mixture is extracted with ethyl acetate and the combined organics are dried over magnesium sulfate and concentrated in vacuo. Chromatography of the crude material over 60 g

of silica gel (elution with 50% ethyl acetate:hexane followed by 70% ethyl acetate:hexane followed by 10% isopropanol in 70% ethyl acetate:hexane followed by ethyl acetate) afforded the title compound (350 mg).
^{1}H NMR ($CDCl_3$) δ 8.63 (d, J = 7 Hz, 1H, ArH), 8.03 (d, J = 8 Hz, 1H, ArH), 7.93 (d, J = 8 Hz, 1H, ArH), 7.76 (t, J = 8 Hz, 1H, ArH), 7.53 (m, 3H, ArH), 7.43 (t, J = 8 Hz, , 1H, ArH), 7.33 (m, 4H, ArH), 6.90 (d, J = 8 Hz, 1H, ArH), 4.98 (bt, J = 7 Hz, 1H, NH), 4.34 (d, J = 7 Hz, 2H, CH_2N), 3.94 (bs, 4H, CH_2N), 3.91 (s, 3H, CH_3O), 2.85 (bs, 9H, CH_3S, CH_2Ar, CH_2N), 2.52 (m, 2H, CH_2N) ppm.

A sample of 200 mg of this material is taken up in methanol (1 mL) and treated with trifluoroacetic acid (0.5 mL). The mixture is purified by medium pressure liquid chromatography (11 mm x 300 mm C18, elution with water followed by 1:1 methanol:water/1% trifluoroacetic acid followed by 5:1 methanol:water/1% trifluoroacetic acid). The collected fractions are concentrated and the residue lyophilized from water to give 121 mg of the title compound as an amorphous solid product.
^{1}H NMR ($CDCl_3$) δ 8.47 (bs, 2H, ArH), 8.09 (d, J = 8 Hz, 1H, ArH), 7.89 (m, 2H, ArH), 7.54 (m, 3H, ArH), 7.24 (m, 3H, ArH), 6.95 (d, J = 8 Hz, 1H, ArH), 4.59 (bs, 1H, NH), 4.07 (d, J = 6 Hz, 2H, CH_2N), 3.75 (s, 3H, CH_3O), 3.69 (bs, 4H, CH_2N), 3.37 (bs, 4H, CH_2N), 2.99 (m, 2H, CH_2Ar), 2.88 (bs, 5H, CH_3S, CH_2N) ppm. Anal. Calcd for $C_{29}H_{33}N_5O_3S$ - 2.5 $C_2F_3HO_2$ - 0.5 H_20: C, 49.45; H, 4.45; N, 8.48. Found: C, 49.37; H, 4.45; N, 8.15.

Example 44

1-(2-Phenyl-1,3-quinazolin-4-yl)-4-[2-(3-(1-succinimidoylmethyl)-4-methoxyphenyl)ethyl]-1,4-piperazine, Trifluoroacetic Acid Salt

Synthesized in a manner similar to Example 43, using 2-[3-(1-succinimidoylmethyl)-4-methoxyphenyl]ethyl-p-toluenesulfonate (1.20 g, 3.00 mmol), prepared as in Intermediate 39, and 1-(2-phenyl-1,3-quinazolin-4-yl)-1,4-piperazine (870 mg, 3.00 mmol) to yield the title compound (849 mg).

^{1}H NMR ($CDCl_3$) δ 9.02 (d, J = 8 Hz, 2H, ArH), 8.44 (d, J = 8 Hz, 1H, ArH), 8.38 (d, 1H, J = 7 Hz, ArH), 8.20 (t, 1H, J = 8 Hz, ArH), 7.97 (m, 3H, ArH), 7.88 (t, J = 7 Hz, 1H, ArH), 7.71 (t, J = 6 Hz, 1H, ArH), 7.62 (d, J = 7 Hz, 1H, ArH), 7.58 (d, J = 8 Hz, 1H, ArH), 7.41 (s, 1H, ArH), 7.24 (d, J = 8 Hz, 1H, ArH), 5.19 (s, 2H, CH_2N), 4.39 (bs, 4H, CH_2N), 4.28 (s, 3H, CH_3O), 3.22 (bs, CH_2CO, CH_2Ar, CH_2N), 3.11 (m, 2H, CH_2N) ppm.

A sample of 200 mg of this material is taken up in methanol (1 mL) and treated with trifluoroacetic acid (0.5 mL). The mixture is purified by medium pressure liquid chromatography (11 mm x 300 mm C18, elution with water followed by 1:1 methanol:water/1% trifluoroacetic acid followed by 5:1 methanol:water/1% trifluoroacetic acid). The collected fractions are concentrated and the residue lyophilized from water to give 175 mg of the title compound as an amorphous solid product.

^{1}H NMR (CD_3OD) δ 8.38 (d, J = 8 Hz, 2H, ArH), 8.27 (d, J = 8 Hz, 1H, ArH), 8.07 (m, 2H, ArH), 7.79 (m, 2H, ArH), 7.68 (t, J = 9 Hz, 2H, ArH), 7.21 (d, J = 8 Hz, 1H, ArH), 7.02 (s, 1H, ArH), 6.96 (d, J = 8 Hz, 1H, ArH), 4.62 (bs, 6H, CH_2N), 3.81 (s, 3H, CH_3O), 3.62 (bs, 4H, CH_2N), 3.42 (m, CH_2N), 3.08 (m, 2H, $ArCH_2$), 2.74 (s, 4H, CH_2CO) ppm. Anal. Calcd for $C_{32}H_{33}N_5O_3 \cdot 2.5\ C_2F_3HO_2 \cdot 0.5\ H_2O$: C, 53.56; H, 4.43; N, 8.44. Found: C, 53.64; H, 4.44; N, 8.37.

Example 45

1-(2-Phenyl-1,3-quinazolin-4-yl)-4-[2-(3-bromo-4-methoxyphenyl)ethyl]-1,4-piperazine, dimaleic acid salt

Synthesized in a manner similar to Example 43, using 2-(3-bromo-4-methoxyphenyl)ethylmethanesulfonate (1.25 g, 4.05 mmol), prepared as in Intermediate 40, and 1-(2-phenyl-1,3-quinazolin-4-yl)-1,4-piperazine (880 mg, 3.03 mmol) to provide the title compound (780 mg) as an oil.

^{1}H NMR ($CDCl_3$) δ 8.57 (d, J = 6 Hz, 2H, ArH), 7.98 (d, J = 8 Hz, 1H, ArH), 7.89 (d, J = 8 Hz, 1H, ArH), 7.71 (t, J = 7 Hz, 1H, ArH), 7.48 (m, 3H, ArH), 7.40 (m, 2H, ArH), 7.12 (d, J = 6 Hz, 1H, ArH), 6.81 (d, J = 6 Hz, 1H, ArH), 3.92 (m, 4H, CH_2N),

3.87 (s, 3H, CH_3O), 2.79 (m, 2H, $ArCH_2$), 2.77 (m, 4H, $ArCH_2$), 2.63 (m, 2H, CH_2N) ppm.

A 750 mg sample of this material is mixed in methanol (3 mL) with 300 mg of maleic acid. Addition of 3 mL of ethyl acetate, chilling to 0°C for 2 h, and collection of the precipitate afforded the title compound (714 mg) as a tan solid.
^1H NMR (CD_3OD) δ 8.43 (d, J = 8 Hz, 2H, ArH), 8.16 (d, J = 8 Hz, 1H, ArH), 8.02 (d, J = 8 Hz, 1H, ArH), 7.97 (t, J = 7 Hz, 1H, ArH), 7.62 (t, J = 8 Hz, 1H, ArH), 7.38 (m, 3H, ArH), 7.29 (d, J = 8 Hz, 1H, ArH), 7.01 (d, J = 8 Hz, 1H, ArH), 6.28 (s, 4H, CH), 4.30 (bs, 4H, CH_2N), 3.60 (s, 4H, CH_2N), 3.42 (m, 2H, CH_2N), 3.07 (m, 2H, CH_2Ar) ppm.
Anal. Calcd for $C_{27}H_{27}N_4OBr$ - 2 $C_4H_4O_4$: C, 57.15; H, 4.80; N, 7.62. Found: C, 56.81; H, 4.89; N, 7.47.

Example 46

1-(2-Phenyl-1,3-quinazolin-4-yl)-4-[2-(3-phenylaminocarbonylaminosulfonyl-4-methoxyphenyl)ethyl]-1,4-piperazine

A solution of 1-(2-phenyl-1,3-quinazolin-4-yl)-4-[2-(3-aminosulfonyl-4-methoxyphenyl)ethyl]-1,4-piperazine (300 mg, 0.60 mmol), prepared as in Example 55, in tetrahydrofuran (2 mL) is stirred at 25°C and is treated in turn with diisopropylethylamine (0.31 mL, 1.77 mmol), phenyl isocyanate (0.20 mL, 1.85 mmol), and 4-dimethylaminopyridine (10 mg). After 30 min at 80°C the mixture is allowed to cool to 25°C and is concentrated in vacuo. The residue is chromatographed on 40 g of silica gel (elution with 70% ethyl acetate:hexane followed by 10% isopropanol in 70% ethyl acetate:hexane followed by 10% methanol - chloroform) to provide the title compound (220 mg) as an amorphous solid.
^1H NMR ($CDCl_3$)δ 8.83 (s, 1H, NH), 8.62 (d, J = 7.5 Hz, 2H, ArH), 8.18 (d, J = 8 Hz, 1H, ArH), 8.02 (d, J = 8 Hz, 1H, ArH), 7.98 (t, J = 7 Hz, 1H, ArH), 7.90 (s, 1H, NH), 7.62 (bs, 4H, ArH), 7.40 (m, 3H, ArH), 7.17 (t, J = 7 Hz, 1H, ArH), 7.10 (m, 1H, ArH), 4.02 (bs, 7H, CH_3O, CH_2N), 2.97 (m, 7H, CH_2N, CH_2N, $ArCH_2$) ppm. Anal. Calcd

for $C_{34}H_{34}N_6O_4S$ - 0.5 H_2O: C, 64.64 ; H, 5.58; N, 13.30. Found: C, 64.60; H, 5.52; N, 12.95.

Example 47

1-(2-Phenyl-1,3-quinazolin-4-yl)-4-[2-(3-(2-tetrahydrofuryl)-4-methoxyphenyl)ethyl]-1,4-piperazine trifluoroacetic acid salt

Synthesized in a manner similar to Example 43, using 2-[3-(2-tetrahydrofuryl)-4-methoxyphenyl]ethyl p-toluenesulfonate (320 mg, 0.85 mmol), prepared as in Intermediate 41,and 1-(2-phenyl-1,3-quinazolin-4-yl)-1,4-piperazine (500 mg, 1.72 mmol) to afford the title comound (310 mg) as an oil.
^1H NMR ($CDCl_3$) δ 8.58 (d, J = 8 Hz, 2H, ArH), 7.98 (d, J = 8 Hz, 1H, ArH), 7.90 (d, J = 8 Hz, 1H, ArH), 7.72 (t, J = 8 Hz, 1H, ArH), 7.47 (m, 3H, ArH), 7.42 (t, J = 7 Hz, 1H, ArH), 7.31 (s, 1H, ArH), 7.08 (d, J = 8 Hz, 1H, ArH), 6.79 (d, 1H, J = 8 Hz, ArH), 5.16 (t, J = 7 Hz, 1H, CHO), 4.91 (m, 6H, CH_2N, CH_2O), 3.80 (s, 3H, CH_3O), 2.81 (t, J = 7 Hz, 2H, $ArCH_2$), 2.80 (m, 4H, CH_2N), 2.70 (m, 2H, CH_2N), 2.40 (m, 1H, CH_2), 1.98 (m, 2H, CH_2), 1.67 (m, 1H, CH_2) ppm.

A 300 mg - sample of this material is treated with 0.5 mL of methanol and 0.5 mL of trifluoroacetic acid. The sample is purified by medium pressure liquid chromatography (11 mm x 300 mm C18, elution with water followed by 3:1 methanol - water/1% trifluoroacetic acid followed by 5:1 methanol - water/1% trifluoroacetic acid). The collected fractions are concentrated and the residue lyophilized from water to give 229 mg of the title compound as an amorphous tan solid.
^1H NMR ($CDCl_3$) δ 8.57 (bs, 2H, ArH), 8.18 (d, J = 8 Hz, 1H, ArH), 7.99 (m, 2H, ArH), 7.60 (m, 4H, ArH), 7.24 (s, 1H, ArH), 7.18 (d, J = 8 Hz, 1H, ArH), 6.97 (d, J = 8 Hz, 1H, ArH), 4.98 (t, J = 7 Hz, 1H, CHO), 4.62 (bs, 2H, CH_2N), 4.00 (dd, J = 7, 6 Hz, 1H, CH_2O), 3.78 (bs, 9H, CH_3O, CH_2N, CH_2O) 3.42 (bs, 4H, CH_2N), 3.00 (bs, 2H, $ArCH_2$), 2.31 (m, 1H, CH_2O), 1.88 (m, 2H, CH_2O), 1.49 (m, 1H, CH_2O) ppm.
Anal. Calcd for $C_{31}H_{34}N_4O_2$ - 2.5 $C_2HO_2F_3$ - 1.5 H_2O: C, 53.60; H, 4.93; N, 6.95. Found: C, 53.49; H, 4.72; N, 6.84.

Example 48

2-Methoxy-5-(2-{4-[2-(2-methoxy-phenyl)-quinazolin-4-yl]-piperazin-1-yl}-ethyl)-benzenesulfonamidemaleate salt

2-(Methoxy-phenyl)-3H-quinazolin-4-one (538mg, 2.13 mmol), prepared as in Intermediate 42, is stirred with $POCl_3$, the mixture is heated to reflux at which time the mixture becomes homogeneous. The solution is cooled to ambient and the $POCl_3$ is removed in vacuo. The residue is taken up in THF (15ml) and treated with 2-methoxy-5-(2-piperazin-1-yl-ethyl)-benzenesulfonamide (768mg, 2.13 mmol) followed by a large excess of triethyl amine (5mL). The solution is brought to reflux for 1h. and cooled to ambient. The solvent is removed in vacuo and the crude material is purified by column chromatography (silica gel; 4% MeOH:methylene chloride). The purified product (630mg, 1.18 mmol) is treated with maleic acid (137mg, 1.18 mmol) to afford the title compound as pale yellow powder.
NMR ^1H (300MHz, DMSO) δ 8.01 (d, 8.4 Hz, 1H), 7.8 (m,2H), 7.6 (m, 2H), 7.58 (m, 1H), 7.42 (m, 2H), 7.12-7.0 (m, 5H), 3.85 (s, 3H), 3.75 (s, 3H), 3.74 (broad s, 4H), 2.77 - 2.55 (m, 8H).
NMR ^{13}C (75 MHz, DMSO) δ 163.58, 160.30, 157.46, 154.39, 152.0, 133.88, 132.72, 130.97, 130.85, 130.18, 129.74, 128.26, 127.63, 125.17, 120.18, 114.22, 112.61, 112.48, 79.21, 59.58, 56.04, 55.80, 52.53, 49.20, 31.34.
Mass Spec; MH^+= 534.2
C,H,N calcd for $C_{28}H_{31}N_5O_4S_1$-1.5 $C_4H_4O_4$-0.5 H2O C: 56.97, H: 5.34, N: 9.77.
Found C: 56.91, H: 5.33, N: 9.52.

Example 49

2-Methoxy-5-(2-{4-[2-(3-trifluoromethyl-phenyl)-quinazolin-4-yl]-piperazin-1-yl}-ethyl)-benzenesulfonamide

Synthesized in a manner similar to Example 48, using 2-(3-Trifluoromethyl-phenyl)-3H-quinazolin-4-one (500mg, 1.7 mmol), prepared as in Intermediate 43,

and 2-methoxy-5-(2-piperazin-1-yl-ethyl)-benzenesulfonamide (620mg, 1.7 mmol) to yield the title compound (900mg, 1.6 mmol).
NMR ^{1}H (300 MHz, DMSO) δ 8.74 (m,2H), 8.0 (d, 8.1Hz, 1H), 7.89-7.72 (m, 4H), 7.63 (d, 2.2Hz, 1H), 7.52 (m, 1H), 7.42 (m, 1H), 7.12 (d, 8.6Hz, 1H), 7.02 (brs, 2H), 3.85 (s, 3H), 3.82 (brs, 4H), 2.77-2.5 (m, 8H).
NMR ^{13}C (75MHz, DMSO) δ 164.08, 156.61, 151.01, 139.16, 133.86, 133.14, 131.86, 131.78, 130.97, 129.78, 128.5, 127.65, 126.82, 126.77, 125.78, 125.46, 124.05, 114.82, 112.58, 79.2, 59.5, 56.03, 52.48, 49.16, 31.38.
Mass Spec: MH^{+}= 572.3
C,H,N calcd for $C_{28}H_{28}N_5O_3S_1F_3$ C: 58.83 H: 4.94, N: 12.25.
Found: C: 58.66, H: 4.99, N: 12.14.

Example 50

2-Methoxy-5-(2-{4-[2-(4-nitro-phenyl)-quinazolin-4-yl]-piperazin-1-yl}-ethyl)-benzenesulfonamide

Synthesized in a manner similar to Example 48, using 2-(4-Nitro-phenyl)-3H-quinazolin-4-one (500mg, 1.87 mmol), prepared as in Intermediate 44,and 2-methoxy-5-(2-piperazin-1-yl-ethyl)-benzenesulfonamide (674mg, 1.87 mmol) to afford the title compound (900mg).
NMR ^{1}H (300MHz, DMSO) δ 8.69 (m,2H), 8.36 (m, 2H), 8.04 (d, 7.9Hz, 1H), 7.93-7.82 (m, 2H), 7.62 (d, 2.2 Hz, 1H), 7.46 (dd, 2.3 Hz, 8.4 Hz, 1H), 7.12 (d, 8.5 Hz, 1H), 7.01 (s,2H), 3.85 (brs, 7H), 2.78-2.5 (m, 8H).
NMR ^{13}C (75 MHz, DMSO) δ 163.96, 156.26, 154.39, 152.00, 148.58, 144.18, 133.88, 133.28, 131.87, 130.96, 129.04, 128.61, 126.19, 125.55, 123.74, 114.76, 112.60, 59.51, 56.03, 52.52, 49.15, 45.64,31.37.
Mass Spec MH^{+}= 549.2
C,H,N calcd. for $C_{27}H_{28}N_6O_5S_1$-0.5 H_2O. C: 58.16 H: 5.24, N: 15.07.
Found C: 58.42, H: 5.24, N: 15.05.

Example 51

2-Methoxy-5-{2-[4-(2-m-tolyl-quinazolin-4-yl)-piperazin-1-yl]-ethyl}-benzenesulfonamide

Synthesized in a manner similar to Example 48, using 2-m-Tolyl-3H-quinazolin-4-one (500mg, 2.1 mmol), prepared as in Intermediate 45, and 2-methoxy-5-(2-piperazin-1-yl-ethyl)-benzenesulfonamide (762mg, 2.1 mmol) to afford the title compound (800mg).

NMR ^{1}H (300 MHz, DMSO), δ 8.29-8.26 (m, 2H), 8.0-7.97 (m, 1H), 7.89-7.76 (m, 2H), 7.62 (d, 2.3 Hz, 1H), 7.52-7.28 (m, 4H), 7.12 (d, 8.5 Hz, 1H), 7.01 (brs, 2H), 3.85 (s, 3H), 3.82 (brs, 4H), 2.7-2.5 (m, 8H).

NMR ^{13}C (75 MHz, DMSO) δ 164.09, 158.28, 154.39, 152.21, 138.13, 137.51, 133.90, 132.93, 131.90, 131.06, 130.97, 128.46, 128.39, 127.65, 125.36, 125.32, 114.7, 112.59, 79.8, 59.57, 56.04, 52.53, 49.23, 31.39, 21.19.

Mas Spec MH^{+}= 518.3

C,H,N calcd. for $C_{28}H_{31}N_5O_3S_1$. C: 64.97, H: 6.04, N: 13.53. Found C: 64.71, H: 6.06, N: 13.45.

Example 52

2-Methoxy-5-{2-[4-(2-pyridin-4-yl-quinazolin-4-yl)-piperazin-1-yl]-ethyl}-benzenesulfonamide

Triazole (1.4g, 20.2mmol) is suspended in acetonitrile (10mL) cooled to 0°C and treated with phosphorous oxychloride (0.42 mL, 4.48 mmol) and triethyl amine (2.8 mL, 20.2mmol). The mixture is stirred at 0°C for 15 min. when the ice bath is removed and 2-Pyridinyl-4-yl-3H-quinazolin-4-one (500mg, 2.24mmol), prepared as in Intermediate 46, is added as a slurry in acetonitrile. The mixture is stirred at 23°C for 2h. when triethylamine (1.8mL, 13.4 mmol) and water (4.7mL) are added with stirring for 15 min. Chloroform (10mL) is added followed by sodium bicarbonate (saturated solution in water). The organic layer is separated and the aqueous is

extracted with chloroform (2 x 15mL). The combined organic extracts are dried with sodium sulfate, filtered and concentrated to an oil. The residue is taken up THF and treated with triethylamine (5mL) and 2-methoxy-5-(2-piperazin-1-yl-ethyl)-benzenesulfonamide (118mg, 0.33 mmol). The resulting solution is heated to reflux overnite, cooled to ambient and concentrated. The residue taken up in chloroform, washed with water and the organic extract is purified by HPLC. Chromatography is performed using a Rainin solvent delivery system and a Rainin Dynamax C18 column. Solvent A consisted of 0.1 % TFA in water. Solvent B consisted of 0.1 % TFA in acetonitrile. The compound is purified using a 0% to 60% B solvent gradient to yield the title compound (22mg.).

NMR H (300 MHz, DMSO) δ 8.9 (d, 1H), 8.75 (d, 1H), 8.4 (m, 2H), 8.22-7.7 (m,4H), 7.6-7.4 (m,2H), 7.0 (d, 1H), 4.0-3.9 (m, 7H).

Mass Spec MH+= 505.0

Example 53

{2-methoxycarbonylmethylsulfamoyl-4-{2-[4-(2-phenyl-quinazolin-4yl)-piperazin-1-yl]-ethyl}-phenoxy)-acetic acid methyl ester

2-Hydroxy-5-{2-[4-(2--phenyl-quinazoline-4-yl)-piperizin-1-yl]-ethyl}-benzenesulfonamide (0.1g, 0.2 mmol), prepared as in Example 55 in a manner similar to Example 23, is dissolved in DMF and treated successively with K_2CO_3 (0.11g, 0.8 mmol), and methyl bromoacetate (0.03 mL, 0.3 mmol). The mixture is stirred overnite, filtered and concentrated to an oil. The crude material is purified by HPLC. Chromatography is performed using a Rainin solvent delivery system and a Rainin Dynamax C18 column. Solvent A consisted of 0.1 % TFA in water. Solvent B consisted of 0.1 % TFA in acetonitrile. The compound is purified using a 15% to 80% B solvent gradient. Lyopholization of the appropriate fraction gave 6mg of the title compound.

NMR ^1H (DMSO, 300MHz) δ 8.5 (m, 2H), 8.05 (d, 1H), 7.9-7.8 (m, 4H), 7.6-7.4 (m,5H), 7.1 (d, 1 H), 7.05 (s, 1H), 5.0 (s, 2H), 4.8 (s, 2H), 4.3 (brs, 4H), 4.03.9 (brs, 6H), 3.8 (s, 3H), 3.7 (s, 3H), 3.2 (brs, 2H).

Mass Spec $[M+H]^+$ 634.3.

Example 54

2-Methoxy-5-{2-[4-(2-phenyl-quinazolin-4-yl)-piperazin-1-yl]-propyl}-benzenesulfonamide

2-Phenyl-4-piperazin-1-yl-quinazoline (479 mg, 1.65 mmol), 2-methoxy-5-(2-oxo-propyl)-benzenesulfonamide (400 mg, 1.65 mmol)(Itoh, Y., *et al*, EP 331943) and titanium tetraisopropoxide (0.64 mL, 2.15 mmol) are stirred for 1h. as a solution in 4mL of THF:EtOH (50:50). Sodium cyanoborohydride (76mg, 1.20 mmol) is added and stirring continued for 24h. The reaction mixture is filtered. The filtrate is evaporated, redissolved in MeOH, and chromatographed by reverse phase HPLC. Chromatography is performed using a Rainin solvent delivery system and a Rainin Dynamax C18 column. Solvent A consisted of 0.1 % TFA in water. Solvent B consisted of 0.1 % TFA in acetonitrile. The compound is purified using a 15% to 80% B solvent gradient. Lyophilization of the appropriate fraction gave 23mg of the title compound.

NMR ^1H (DMSO, 300MHz) δ 8.4 (m,2H), 8.2 (d, 2H), 8.01 (m, 3H), 7.8-7.4 (m, 7H), 7.2 (d, 2H), 7.0 (s, 1H), 3.9 (s, 3H), 3.85-3.5 (m, 9H), 3.3 (m, 1H), 2.8 (m, 1H), 1.2 (d, 3H).

Mass Spec $[M+H]^+$= 518.0

Example 55

2-methoxy-5-{2-[4-(2-phenyl-quinazolin-4-yl)-piperazin-1-yl]-ethyl}-benzenesulfonamide maleate

A suspension of 2-phenyl-4-piperazin-1-yl-quinazoline (1.33g, 4.6 mmol), prepared as in Intermediate 49, 5-(2-chloroethyl)-2-methoxy-benzenesulfonamide (1.3g, 5.98 mmol), prepared as in Intermediate 48, K_2CO_3 (1.91 g, 13.8 mmol), and NaI (150 mg) in CH_3CN (100 mL) is heated at 95° C for 18h. The reaction mixture is filtered and the solids washed with EtOH. The solvent is evaporated and the residue is purified by chromatography on silica using 4% MeOH : CH_2Cl_2 as eluent to afford

the product as a pale yellow foam (1.23 g, 53%). A solution of the product (1.23 g, 2.44 mmol) in hot EtOH (10 mL) is treated with a solution of maleic acid (283 mg, 2.44 mmol) in EtOH (3 mL). The solvent is evaporated, and the residue crystallized from EtOH and Et_2O to afford the title compound as an off white solid.

^1H NMR (DMSO-d6) δ 8.51 (m, 2H), 8.08 (d, 1H, J = 8.3 Hz), 7.92 (m, 2H), 7.69 (d, 1H, J = 2.2 Hz), 7.52 (m, 5H), 7.18 (d, 1H, J = 8.5 Hz), 7.05 (s, 2H), 6.06 (s, 2H), 3.87 (s, 3H), 3.31 (m, 10H), 2.99 (m, 2H).

$C_{31}H_{33}N_5O_7S$-H2O requires C: 58.39, H: 5.53, N: 10.98; found C: 58.73, H: 5.47, N: 10.79.

Example 56

2-methoxy-5-{2-[4-(8-chloro-2-phenyl-quinazolin-4-yl)-piperazin-1-yl]-ethyl}-benzenesulfonamide

A solution of 8-chloro-2-phenyl-3H-quinazolin-4-one (68 mg, 0.26 mmol), prepared as in Intermediate 51, in $POCl_3$ (10 mL) is heated at reflux for 30 min. The $POCl_3$ is removed by rotary evaporation, and the residue partitioned between $CHCl_3$ (100 mL) and H_2O (50 mL). The organic layer is dried (Na_2SO_4) and concentrated to a yellow solid. This solid is taken up in THF (10 mL), treated with 2-methoxy-5-(2-piperazin-1-yl-ethyl)-benzenesulfonamide dihydrochloride (145 mg, 0.39 mmol) and Et_3N (2 mL), prepared as in Intermediate 50, and heated at reflux for 15 h. The solvent is evaporated, and the residue purified by chromatography on silica using 3% MeOH:$CHCl_3$ as eluent to afford the title compound as a tan solid (52 mg, 37%).

^1H NMR (DMSO-d6) δ 8.50 (m, 2H), 7.96 (m, 2H), 7.61 (d, 1H, J = 2.2 Hz), 7.52 (m, 3H), 7.45 (m, 2H), 7.10 (d, 1H, J = 8.6 Hz), 7.00 (broad s, 2H), 3.85 (broad s, 7H), 2.78 (m, 2H), 2.68 (m, 4H), 2.56 (m, 2H).

C27H28N5O3SCl requires C: 60.27, H: 5.25, N: 13.02; found :C: 60.07, H: 5.27, N: 12.83.

FAB MS m/z found 538 (MH+)

Example 57

2-Methoxy-5-{2-[4-(7-chloro-2-phenyl-quinazolin-4-yl)-piperazin-1-yl]-ethyl}-benzenesulfonamide

Synthesized in a manner similar to Example 56, using 7-chloro-2-phenyl-3H-quinazolin-4-one (270 mg, 1.05 mmol), prepared as in Intermediate 52, and 2-methoxy-5-(2-piperazin-1-yl-ethyl)-benzenesulfonamide dihydrochloride (558 mg, 1.5 mmol), prepared as in Intermediate 50, to afford the title compound as a yellow solid (260 mg).

^{1}H NMR (DMSO-d6) δ 8.45 (m, 2H), 8.01 (d, 1H, J = 9 Hz), 7.89 (d, 1H, J = 2.2 Hz), 7.61 (d, 1H, J = 2.2 Hz), 7.56 - 7.42 (m, 5H), 7.11 (d, 1H, J = 8.6 Hz), 7.13 (broad s, 2H), 3.86 (br s, 7H), 2.78 (m, 2H), 2.67 (m, 4H), 2.56 (m, 2H).

C27H28N5O3SCl requires C: 60.27, H: 5.25, N: 13.02; found C:60.05, H: 5.36, N: 12.80

FAB MS m/z found 538 (MH+)

Example 58

2-methoxy-5-{2-[4-(2-cyclohexyl-quinazolin-4-yl)-piperazin-1-yl]-ethyl}-benzenesulfonamide maleate

Synthesized in a manner similar to Example 56, using 2-cyclohexyl-3H-quinazolin-4-one (300 mg, 1.31 mmol), prepared as in Intermediate 53, and 2-methoxy-5-(2-piperazin-1-yl-ethyl)-benzenesulfonamide dihydrochloride (488 mg, 1.31 mmol), prepared as in Intermediate 50, to afford the title compound as a pale orange solid (534 mg).

^{1}H NMR (DMSO-d6) δ 8.02 (d, 1H, J = 8.0 Hz), 7.79 (m, 2H), 7.67 (s, 1H), 7.49 (m, 2H), 7.16 (d, 1H, J = 8.3 Hz), 7.05 (s, 2H), 6.04 (s, 2H), 3.95 (m, 4H), 3.87 (s, 3H), 3.25 (m, 6H), 2.95 (m, 2H), 2.76 (m,1H), 1.95 (m, 2H), 1.77 (m, 2H), 1.62 (m, 3H), 1.35 (m, 3H).

C31H39N5O7S requires C: 59.5, H: 6.28, N: 11.19; found C: 59.3, H:6.25, N:11.04.

FAB MS m/z found 510 (MH+)

Example 59

2-methoxy-5-{2-[4-(2-(1H-pyrrol-2-yl)-quinazolin-4-yl)-piperazin-1-yl]-ethyl}-benzenesulfonamide

Synthesized in a manner similar to Example 56, using 2-(1H-pyrrol-2-yl)-3H-quinazolin-4-one (405 mg, 1.9 mmol), prepared as in Intermediate 54, and 2-methoxy-5-(2-piperazin-1-yl-ethyl)-benzenesulfonamide dihydrochloride (707 mg, 1.9 mmol), prepared as in Intermediate 50, to afford the title compound as a tan solid (410 mg).

^{1}H NMR (CDCl3) δ 7.66 (m, 3H), 7.51 (dt, 1H, J = 8.3, 1.2 Hz), 7.25 (dd, 1H, J = 8.6, 2.2 Hz), 7.18 (dt, 1H, J = 8.0, 1.0 Hz), 6.98 (d, 1H, J = 2.9 Hz), 6.83 (m, 2H), 6.19 (m, 1H), 4.99 (s, 2H), 3.85 (s, 3H), 3.68 (m, 4H), 2.70 (m, 2H), 2.58 (m, 4H), 2.51 (m, 2H).

FAB MS m/z found 493 (MH+)

Example 60

2-methoxy-5-{2-[4-(2-chloro-quinazolin-4-yl)-piperazin-1-yl]-ethyl}-benzenesulfonamide hydrochloride

A solution of 2,4-dichloroquinazoline (160 mg, 0.8 mmol) in THF (5 mL) is treated with a solution of 2-methoxy-5-(2-piperazin-1-yl-ethyl)-benzenesulfonamide dihydrochloride, prepared as in Intermediate 50, and Et_3N (0.22 mL) in MeOH (5 mL) and stirred at 23 C for 18h. The reaction mixture is filtered and the white solid is washed with EtOAc to afford the title compound (290 mg).

^{1}H NMR (DMSO-d6) δ 11.12 (s, 1H), 7.90 (t, 1H, J = 8 Hz), 7.78 (d, 1H, J = 8 Hz), 7.67 (s, 1H), 7.60 (t, 1H, J = 7 Hz), 7.48 (d, 1H, J = 9Hz), 7.18 (d, 1H, J = 8 Hz), 7.06 (s, 2H), 4.47 (m, 2H), 3.87 (s, 3H), 3.75 (m, 4H), 3.38 (m, 4H), 3.10 (m, 2H).

$C_{21}H_{25}N_5O_3SCl_2$ - 0.5 H_2O) requires C: 49.71, H: 5.16, N: 13.80; found C: 49.82, H: 5.06, N: 14.05.

FAB MS m/z found 462.3 (MH+)

Example 61

2-methoxy-5-{2-[4-(quinazolin-4-yl)-piperazin-1-yl]-ethyl}-benzenesulfonamide

A solution of 2-methoxy-5-{2-[4-(2-chloro-quinazolin-4-yl)-piperazin-1-yl]-ethyl}-benzenesulfonamide hydrochloride (210 mg, 0.45 mmol), prepared as in Example 60, in EtOH (50 mL) and EtOAc (50 mL) is treated with NaOAc (37 mg, 0.45 mmol) and 10% Pd/C (200 mg)and hydrogenated at 40 psi for 24h. The catalyst is removed by filtration through celite, and the solvent evaporated. The residue is purified by chromatography on silica using 5% MeOH: CH_2Cl_2 as eluent to afford the product as a yellow oil (41 mg, 21%). The oil (41 mg, 0.1 mmol) in hot EtOH is treated with a solution of maleic acid (12 mg, 0.1 mmol) in warm EtOH. The precipitated product solid is collected and dried to afford the title compound as a pale yellow solid.

^1H NMR (DMSO-d6) δ 8.72 (s, 1H), 8.05 (d, 1H, J = 8.1 Hz), 7.96 (s, 2H), 7.66 (s, 1H), 7.62 (m, 1H), 7.48 (d, 1H, J = 8.3 Hz), 7.17 (d, 1H, J = 8.3 Hz), 7.05 (s, 2H), 6.05 (s, 2H), 3.87 (s, 3H), 3.31 (m, 10H), 2.96 (m, 2H).

$C_{25}H_{29}N_5O_7S$ requires C:55.24, H:5.38, N:12.88; found C:55.10, H:5.45, N:12.59.

FAB MS m/z found 428 (MH+)

Example 62

(R) 2-methoxy-5-{2-[3-(2-(3-chloro-4-fluoro-phenyl)-quinazolin-4-yl amino)-pyrrolidin-1-yl]-ethyl}-benzenesulfonamide

Synthesized in a manner similar to Example 56, using 2-(3-chloro-4-fluoro-phenyl)-3H-quinazolin-4-one (640 mg, 2.3 mmol), prepared as in Intermediate 55, and (R(-5-[2-(3-amino-pyrrolidin-1-yl)-ethyl]-2-methoxy-benzenesulfonamide (596 mg, 1.6 mmol), prepared as in Intermediate 47, to yield the title compound as a tan solid (200 mg).

^{1}H NMR (DMSO-d6) δ 11.34 (br s, 1H), 8.89 (m, 0.5 H), 8.76 (m, 1.5 H), 8.57 (m, 1H), 8.17 (d, 1H, J = 7.6 Hz), 8.04 (t, 1H, J = 7.1 Hz), 7.73 (m, 3H), 7.54 (d, 1H, J = 8.6 Hz), 7.21 (dd, 1H, J = 8.5, 3.6 Hz), 7.09 (s, 2H), 5.41 (m, 0.5H), 5.29 (m, 0.5 H), 4.15 (m, 1H), 3.91 (s, 3H), 3.59 (m, 5H, obscured by H_2O), 3.10 (m, 2H), 2.72 (m, 1H), 2.39 (m, 1H).
FAB MS m/z 556.5 (MH+)

Example 63

2-methoxy-5-{2-[4-(5-chloro-2-phenyl-quinazolin-4-yl)-piperazin-1-yl]-ethyl}-benzenesulfonamide trifluoroacetate

Synthesized in a manner similar to Example 56, using 5-chloro-2-phenyl-3H-quinazolin-4-one (460 mg, 1.8 mmol), prepared as in Intermediate 56, and 2-methoxy-5-(2-piperazin-1-yl-ethyl)-benzenesulfonamide dihydrochloride (819 mg, 2.2 mmol), prepared as in Intermediate 50, to afford the product as a pale pink powder (600 mg).
^{1}H NMR (DMSO-d6) δ 8.46 (m, 2H), 7.88 (m, 1H), 7.81 (t, 1H, J = 7.7 Hz), 7.66 (m, 2H), 7.53 (m, 4H), 7.18 (m, 1H), 7.04 (br s, 2H), 4.40 (m, 1H), 4.18 (m, 1H), 3.86 (m, 5H), 3.50 (m, 3H), 3.25 (m, 2H), 3.1 - 2.92 (m, 3H).
$C_{31}H_{30}N_5O_7SClF_6$-H_2O requires C:47.48, H: 4.11, N: 8.93, found C: 47.40, H: 3.94, N: 8.75.

Example 64

2-methoxy-5-{2-[4-(6-methoxy-2-phenyl-quinazolin-4-yl)-piperazin-1-yl]-ethyl}-benzenesulfonamide trifluoroacetate

Synthesized in a manner similar to Example 56, using 6-methoxy-2-phenyl-3H-quinazolin-4-one (320 mg, 1.3 mmol), prepared as in Intermediate 57, and 2-methoxy-5-(2-piperazin-1-yl-ethyl)-benzenesulfonamide dihydrochloride (532 mg, 1.43 mmol), prepared as in Intermediate 50, to afford the title compound as an off-white powder (90 mg).

^{1}H NMR (DMSO-d6) δ 10.8 broad, 1H), 8.60 (,m, 2H), 8.09 (d, 1H, J = 9 Hz), 7.82 (d, 1H, J = 1.9 Hz), 7.68 (m, 5H), 7.44 (d, 1H, J = 2.5 Hz), 7.33 (d, 1H, J = 8.6 Hz), 7.20 (s, 2H), 4.69 (m, 2H), 4.09 (s, 3H), 4.01 (s, 3H), 3.85 (m, 4H), 3.52 (m, 4H), 3.20 (m, 2H).

$C_{32}H_{33}N_5O_8F_6S$ - 0.5 H_2O requires C: 49.87, H: 4.45, N: 9.09, found: C: 50.01, H: 4.55, N: 9.25.

FAB MS m/z 534.1 (MH+).

Example 65

3,7-dimethyl-1-{3-[4-(2-phenyl-quinazolin-4-yl)-piperazin-1-yl]-propyl}-3,7-dihydropurine-2,6-dione trifluoroacetate

A solution of 2-phenyl-4-piperazin-1-yl-quinazoline (1g, 3.44 mmol), 1-(3-chloropropyl)theobromine (883 mg, 3.44 mmol), K_2CO_3 (954 mg, 6.9 mmol), and NaI (100 mg) in CH_3CN (15 mL) is heated at reflux 95 C for 15h. The solvent is evaporated and the residue purified by reverse phase HPLC (gradient elution, 10 - 60 % CH_3CN in H_2O with 0.1 % TFA). The appropriate fractions are lyophilized to afford the title compound as an off-white solid (432 mg).

^{1}H NMR (DMSO-d6) δ 8.46 (m, 2H), 7.99 (m, 2H), 7.85 (m, 2H), 7.49 (m, 4H), 3.94 (t, 2H, J = 7.1 Hz), 3.87 (s, 3H), 3.76 (m, 4H), 3.40 (s, 3H), 2.59 (m, 4H), 2.43 (m, 2H), 1.76 (m, 2H).

FAB MS m/z 511 (MH+)

Example 66

1-methyl-5-{4-[4-(2-phenyl-quinazolin-4-yl)-piperazin-1-yl]-butylidene}-imidazolidine-2,4-dione

A solution of 4-[4[(2-phenyl-quinazolin-4-yl)-piperazin-1-yl]-butyraldehyde (466 mg, 1.3 mmol), prepared as in Intermediate 58, diethyl 1-methyl-2,4-dioxoimidazolidine-5-phosphonate (for preparation see *J Org Chem* , 56, 6897 (1991)) (400 mg, 1.6 mmol), and LiCl (68 mg, 1.6 mmol) in CH_3CN (16 mL) is

treated with DBU (0.19 mL, 1.3 mmol) and stirred at 23 C for 18h. The solvent is evaporated and the residue purified by chromatography on silica using 3% CH_3OH:CH_2Cl_2 as eluent to afford the title compound (2:1 mixture of olefin isomers) as a white solid (130 mg).

^1H NMR ($CDCl_3$) δ 8.40 (m, 2H), 7.83 (d, 1H, J = 8.3 Hz), 7.75 (d, 1H, J = 8.0 Hz), 7.58 (t, 1H, J = 7.1 Hz), 7.32 (m, 3H), 7.27 (t, 1H, J = 8.1 Hz), 5.72 (t, 0.33H, J = 8.3 Hz), 5.29 (t, 0.66H, J = 8.1 Hz), 3.80 (m, 4H), 2.92 (s, 3H), 2.62 (m, 6H), 2.41 (m, 2H), 1.64 (m, 2H).

FAB MS m/z 457.2 (MH+).

Example 67

2-Methoxy-5-{3-[4-(2-phenyl-quinzolin-4-yl)-piperazin-1-yl]-propyl}-benzenesulfonamide

5-(3-chloro-propyl)-2-methoxy-benzenesulfonamide (0.44 g, 1.7 mmol), prepared as in Intermediate 59, diisopropylethylamine (0.5 mL, 2.8 mmol) and sodium iodide (170 mg, 1.1 mmol) are added to a solution of 2-phenyl-4-piperazine-1-yl-quinazoline (0.32 g, 1.1 mmol) in dioxane (10 mL), and the solution is heated at reflux for 36 h. After cooling, saturated sodium bicarbonate solution is added to the reaction mixture which is then extracted with ethyl acetate. The combined organic layers are dried with magnesium sulfate, filtered and concentrated to give a yellow residue. The residue is purified by recrystallization from hot ethyl acetate. The crystals are washed with chloroform and dried in a vacuum oven to give the title compound.

^1H NMR (DMSO-d_6) δ 8.50-8.47 (m, 2H), 8.00 (d, 1H, *J* = 8 Hz), 7.89-7.78 (m, 2H), 7.59 (s, 1H) 7.54-7.46 (m, 4H), 7.42 (dd, 1H, *J*= 2.2, 8 Hz), 7.11 (d, 1H, 9 Hz), 7.01 (s, 2H), 3.86-3.83 (m, 7H), 2.68-2.53 (m, 6H), 2.36-2.32 (m, 2H), 1.77-1.73 (m, 2H);

FAB MS *m / z* found 518 (MH^+).

Anal. Calcd. for $C_{28}H_{32}N_5O_3S$: C, 64.97; H, 6.04; N, 13.53. Found C, 63.53; H, 5.92; N, 13.16.

Example 68

2-Methoxy-N-methyl-5-{2-[4-(2-phenyl-quinazolin-4-yl)-piperazin-1-yl]-ethyl}-benzenesulfonamide bismaleate

Synthesized in a manner similar to Example 67, using 5-(2-Chloro-ethyl)-2-methoxy-N-methyl-benzenesulfonamide (1.0 g, 4 mmol), prepared as in Intermediate 60, and 2-phenyl-4-piperazine-1-yl-quinazoline (0.74 g, 2.5 mmol)to yield the title compound (0.27 g):

^{1}H NMR (DMSO-d$_6$) δ 8.52-8.49 (m, 2H), 8.09 (d, 1H, J = 8 Hz), 7.96-7.85 (m, 2H), 7.68 (d, 1H, J = 2 Hz), 7.60-7.52 (m, 5H), 7.21 (d, 1H, J = 8 Hz), 7.01 (d, 1H, J = 5 Hz), 6.13 (s, 4H), 3.87 (s, 5H). 3.51-3.36 (m, 6H), 3.06-3.01 (m, 4H), 2.37 (d, 3H, J = 5 Hz);

FAB MS m / z found 518 (MH^+).

Anal. Calcd.for $C_{36}H_{39}N_5O_{11}S \cdot 0.5\ H_2O$: C, 57.67; H, 5.24; N, 9.34. Found: C, 56.88; H, 5.26; N, 9.28.

Example 69

2-Methoxy-N,N-dimethyl-5-{2-[4-(2-phenyl-quinazolin-4-yl)-piperazin-1-yl]-ethyl}-benzenesulfonamide bismaleate

Synthesized in a manner similar to Example 67, using 5-(2-chloro-ethyl)-methoxy-N,N-dimethyl-benzenesulfonamide (1.0 g, 3.6 mmol), prepared as in Intermediate 61,and 2-phenyl-4-piperazine-1-yl-quinazoline (0.70 g, 2.4 mmol) to give the title compound (0.76 g):

^{1}H NMR (DMSO-d$_6$) δ 8.50-8.47 (m, 2H), 8.00 (d, 1H, J = 8 Hz) 7.89-7.78 (m, 2H), 7.62 (s, 1H), 7.53-7.50 (m, 5H), 7.17 (d 1H, J = 9 Hz), 3.84-3.82 (m, 7H), 2.82-2.75 (m, 2H), 2.70 (s, 10H), 2.63-2.56 (m, 2H).

Anal. Calcd. for $C_{37}H_{41}N_5O_{11}S$: C, 58.18; H, 5.41; N, 9.17. Found: C, 57.96, H, 5.36, N, 9.33.

Example 70

N-Acetyl-2-methoxy-5-{2-[4-(2-phenyl-quinazolin-4-yl)-piperazin-1-yl]-ethyl}-benzenesulfonamide

Acetic anhydride (0.6 mL, 6 mmol) and concentrated sulfuric acid (1 drop) are added to a stirring solution of 2-methoxy-5-{2-[4-(2-phenyl-quinazolin-4-yl)-piperazin-1-yl]-ethyl}-benzenesulfonamide maleate (0.20 g, 0.4 mmol), prepared as in Example 55, in dioxane (5 mL). The solution is then heated to 60°C for 4 h, The mixture is cooled and saturated sodium bicarbonate solution is added. Next, the material is extracted with ethyl acetate. The organic layers are combined and dried with magnesium sulfate, filtered and concentrated. The residue is purified by silica gel chromatography with an eluant of methanol:methylene chloride (gradient of 1:19 to 1:9) to give the title compound as an off-white solid (27 mg):
^{1}H NMR (DMSO-d$_6$) δ 11.90 (s, 1H), 8.50-8.47 (m, 2H), 8.00 (d, 1H, J = 9 Hz), 7.89-7.78 (m, 2H), 7.70 (d, 1H, J = 2 Hz), 7.56-7.49 (m, 5H), 7.15 (d, 1H, J = 8 Hz), 3.87-3.84 (m, 7H), 2.84-2.79 (m, 2H), 2.70 (s, 4H). 2.62-2.57 (m, 2H), 1.9 (s, 3H); FAB MS m/z found 546 (MH^+).
Anal. Calcd. for $C_{29}H_{31}N_5O_4S \cdot 0.5\ H_2O$: C, 62.80; H, 5.82; N, 12.63. Found: C, 62.79; H, 5.79; N, 12.54.

Example 71

N-Acetyl-2-methoxy-N-methyl-5-{2-[4-(2-phenyl-quinazolin-4-yl)-piperazin-1-yl]-ethyl}-benzenesulfonamide bistrifluoroacetate

Acetic anhydride (0.37 mL, 3.9 mmol) and concentrated sulfuric acid (1 drop) are added to a stirring solution of 2-methoxy-N-methyl-5-{2-[4-(2-phenyl-quinazolin-4-yl)-piperazin-1-yl]-ethyl}-benzenesulfonamide (0.20 g, 0.28 mmol), prepared as in Example 68, in dioxane (5 mL), and the mixture is heated to 60°C for 5 h. After cooling, the mixture is concentrated and azeotroped with toluene. The residue is

purified by reverse phase HPLC using acetonitrile:water (5% to 40% gradient over 30 min) as the eluant to give the title compound (90 mg):
^{1}H NMR (DMSO-d6) δ 8.81 (d, 2H, *J* = 7 Hz), 8.66 (d, 1H, *J* = 8 Hz), 8.47 (d, 2H, *J* = 4 Hz), 8.36 (s, 1H), 8.21-8.05 (m, 5H), 7.66 (d, 1H, *J* = 8 Hz), 5.06 (s, 4H), 4.36 (s, 3H), 4.07 (s, 4H), 3.93-3.87 (m, 2H), 3.71-3.60 (m, 5H), 2.72 (s, 3H); FAB MS *m / z* found 560 (MH^+).
Anal. Calcd. for $C_{30}H_{33}N_5O_4S \cdot C_2HO_2F_3$: C, 51.84; H, 4.48; N, 8.89. Found: C, 52.53; H, 4.72; N, 9.10.

Example 72

2-{3-[4-(2-phenyl-quinazolin-4-yl)-piperazin-1-yl]-propyl}-isoindole-1,3 dione

N-(3-Bromopropyl)phthalamide (16.2 g, 56 mmol) is added to a stirring solution of 2-phenyl-4-piperazine-1-yl-quinazoline (16.0 g, 55 mmol), prepared as in Intermediate 49, in dry acetonitrile (275 mL). Next the mixture is heated to just below reflux and potassium carbonate (22.8 g, 165 mmol) and sodium iodide (4.1 g, 28 mmol) are added. The mixture is refluxed for 16 h. After cooling, the reaction mixture is concentrated. The residue is dissolved in ethyl acetate and is washed with water and then brine. The organic layer is dried over magnesium sulfate, filtered and concentrated until solid began to form. The mixture is left at room temperature for 16 h and is then filtered. The white solid is washed with ethyl acetate and dried to give the title compound (21.18 g):
^{1}H NMR (DMSO-d6) δ 8.45-8.42 (m, 2H), 7.92 (d, 1H, *J* = 8 Hz), 7.87-7.83 (m, 3H), 7.81-7.75 (m, 4H) 3.68-3.62 (m, 6H), 2.47-2.46 (m, 4H), 2.40 (t, 2H, *J* = 6 Hz), 1.86 (p, 2H, *J* = 6 Hz);
FAB MS *m / z* found 478 (MH^+).
Anal. Calcd. for $C_{29}H_{27}N_5O_2$: C, 72.94; H, 5.70; N, 14.67. Found: C, 73.00; H, 5.70; N, 14.61.

Example 73

3-{2-[4-(2-phenyl-quinazolin-4-yl)-piperazin-1-yl]-ethoxy}-benzamide

Diisopropylethylamine (0.95 mL, 5.5 mmol), 3-(2-chloro-ethoxy)-benzamide (0.44 g, 2.2 mmol), prepared as in Intermediate 62, and sodium iodide (0.16 g, 1.1 mmol) are added to a stirring solution of 2-phenyl-4-piperazine-1-yl-quinazoline (0.40 g, 1.1 mmol) in dioxane (10 mL). The reaction mixture is refluxed for 16 h. After cooling, the reaction mixture is diluted with sodium bicarbonate solution and washed with ethyl acetate. The organic layers are combined and dried with magnesium sulfate, filtered and concentrated. The residue is purified by silica gel chromatography with an eluant of methanol:methylene chloride (1:20) to give the title compound (80 mg):

^{1}H NMR ($CDCl_3$) δ 8.57-8.54 (m, 2H), 7.94 (dd, 2H, J = 9 , 2 Hz), 7.72 (t, 1H, J = 9 Hz), 7.75-7.32 (m, 7H), 7.13-7.09 (m, 1H), 4.23 (t, 2H, J = 6 Hz), 3.91(t, 4H, J = 4 Hz) 2.93 (t, 2H J = 5 Hz) 2.83 (t, 4H, J = 5 Hz).

Anal. Calcd. for $C_{27}H_{27}N_5O_2$: C,71.50; H, 6.00; N, 15.44. Found: C, 71.29; H, 6.05; N, 15.37.

Example 74

1,3-Dimethyl-9-{2-[4-(2-phenyl-quinazolin-4-yl)-piperazin-1-yl]-ethyl}-3,9-dihydro-purine-2,6-dione bistrifluoroacetate

7-(2-Chloroethyl)theophylline (0.62 g, 2.6 mmol)(Aldrich), sodium iodide (0.25 g, 1.7 mmol) and diisopropylethylamine (1.2 mL, 6.8 mmol) are added to a stirring mixture of 2-phenyl-4-piperazine-1-yl-quinazoline dihydrochloride (0.60 g, 1.7 mmol) in dioxane (20 mL). The mixture is refluxed for 16 h. After cooling, the reaction mixture is diluted with sodium bicarbonate solution and then washed with ethyl acetate. The organic layers are combined, dried over magnesium sulfate, filtered and concentrated. The residue is purified by reverse phase HPLC using an eluant of acetonitrile: water (5% to 40% gradient over 30 min) to give the title compound (73 mg):

^{1}H NMR (CD_3OD) δ 8.34-8.31 (m, 2H), 8.24 (d, 1H, J = 8 Hz), 8.08-8.01 (m, 3H), 7.73 (dt, 4H, J = 25, 7 Hz), 4.54 (t, 4H, J = 5 Hz), 3.56 (s, 3H), 3.37 (s, 3H), 3.19 (t, 4 H, J = 5 Hz);

FAB MS *m / z* found 497 (MH^+).
Anal. Calcd. for $C_{27}H_{28}N_8O_2 \cdot 0.5\ H_2O \cdot 2\ C_2HF_3O_2$: C, 50.75; H, 4.26; 15.27.
Found C, 50.80; H, 4.26; N, 15.37.

Example 75

4-{4-[2-(7-Methoxy-1,2,3,4-tetrahydro-naphthalen-2-yl)-ethyl]-piperazin-1-yl}-2-phenyl-quinazoline

7-Methoxy-2-tetralone (1.0 mL, 1.7 mmol)(Aldrich), acetic acid (1.2 mL, 0.21 mol), and molecular sieves are added to a stirring solution of 2-phenyl-4-piperazine-1-yl-quinazoline (1.0 g, 3.4 mmol) in a mixture of tetrahydrofuran and methanol (1:1, 4 mL). The reaction mixture is cooled to 0°C in an ice bath and sodium cyanoborohydride (0.21 g, 3.4 mmol) is added. The reaction is stirred at 0°C for 3 h and is then allowed to warm to room temperature. The mixture is filtered and the solid washed with ethyl acetate. The filtrate is washed with 1N sodium hydroxide followed by brine. The organic layers are combined, dried over magnesium sulfate, filtered and concentrated. The residue is purified by silica gel chromatography with an eluant of ethyl acetate:hexane (30% to 70% gradient) to give the title compound (470 mg):
^1H NMR (DMSO-d_6) δ 8.50-8.47 (m, 2H), 8.01 (d, 1H, J = 8 Hz), 7.89-7.78 (m, 2H), 7.53-7.49 (m, 4H), 6.98-6.94 (m, 1H), 6.66-6.65 (m, 2H), 3.85 (s, 4H), 3.68 (s, 3H), 2.86-2.67 (m, 9H), 2.05-2.01 (m, 1H), 1.61 1.55 (m, 1H);
FAB MS *m / z* found 476 (MH^+).
Anal. Calcd. for $C_{29}H_{30}N_4O$: C, 77.30; H, 4.26; 15.27. Found: C, 77.06; H, 6.80; N, 12.23.

Example 76

4-{4-[2-(6-Methoxy-1,2,3,4-tetrahydro-naphthalen-2-yl)-ethyl]-piperazin-1-yl}-2-phenyl-quinazoline bistrifluoroacetate

Synthesized in a manner similar to Example 75, using 6-Methoxy-2-tetralone (1.0 mL, 1.7 mmol)(Lancaster), and 2-phenyl-4-piperazine-1-yl-quinazoline (1.0 g, 3.4 mmol) to give the title compound (115 mg):
^{1}H NMR (DMSO-d_6) δ 8.50-8.47 (m, 2H), 8.14 (d, 1H, J = 8 Hz), 7.98-7.88 (m, 2H), 7.63-7.54 (m, 4H), 7.04 (d, 1H, J = 8 Hz), 6.76-6.71 (m, 2H), 4.65-4.60 (m, 4H) 3.70 (s, 3H), 3.66-3.45 (m, 3H), 3.13-2.82 (m, 6H), 2.40-2.29 (m, 1H), 1.89-1.74 (m, 1H); FAB MS m/z found 451 (MH+).
Anal. Calcd. for $C_{29}H_{30}N_4O \cdot 2\ C_2HF_3O_2 \cdot 0.75\ H_2O$: C, 58.41; H, 4.75; N 8.26. Found: C, 57.14; H, 4.82; N, 8.13.

Example 77

2,2,3,3,-Tetramethyl-cyclopropanecarboxylic acid {3-[4-(2-phenyl-quinazolin-4-yl)-piperazin-1-yl]-propyl}-amide maleate

2,2,3,3-Tetramethylcyclopropanecarboxylic acid (0.10 g, 0.7 mmol), diisopropylethylamine (0.4 mL, 2.1 mmol), and bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (0.36 g, 0.77 mmol) are added to a stirring solution of 3-[4-(2-Phenyl-quinazolin-4-yl)-piperazin-1-yl]-propylamine (0.25 g, 0.7 mmol), prepared as in Intermediate 63, in dimethylformamide (3.0 mL). After 2 h the reaction is diluted with water and washed with ethyl acetate and chloroform. The organic layers are combined, dried over sodium sulfate, filtered and concentrated. The residue is purified by silica gel chromatography using an eluant of methanol:methylene chloride (1:19). The maleic acid salt is made by dissolving the product in a minimal amount of boiling ethyl acetate and adding maleic acid (25 mg, 0.21 mmol) in methanol (0.2 mL). The solid which formed upon cooling is filtered and dried in a vacuum to give 2,2,3,3,-tetramethyl-cyclopropanecarboxylic acid {3-[4-(2-phenyl-quinazolin-4-yl)-piperazin-1-yl}-propyl-amide (83 mg, 20 %): ^{1}H NMR (CD_3OD) δ 8.48-8.46 (m, 2H), 8.07(d, 1H, J = 8 Hz), 7.98 (d, 1H, J = 8 Hz), 7.88-7.85 (m, 1H), 7.59 (t, 1H, J = 7 Hz), 7.51-7.49 (m, 3H), 6.23 (s, 2H), 3.45 (s, 4H), 3.30-3.28 (m, 4H), 3.12 (t, 2H, J = 7 Hz), 1.96 (p, 2H, J = 7 Hz), 1.26 (s, 6H), 1.18 (s, 6H), 1.08 (s, 1H); FAB MS m/z found 472 (MH^+). Anal. Calcd. for $C_{29}H_{37}N_5O \cdot 0.33\ H_2O \cdot 1\ C_4H_4O_4$: C, 66.76; H, 7.07; N, 11.08. Found: C, 66.64; H, 6.89; N, 11.83.

Example 78

Tetrahydro-furan-2-carboxylic acid [2-[4-(2-phenyl-quinazolin-4-yl)-piperazin-1-yl]-ethyl)-amide bistrifluoroacetate

2-Tetrahydrofuroic acid (0.11 mL, 1.1 mmol), diisopropylethylamine (0.2 mL, 1.1 mmol), and bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (0.76 g, 1.7 mmol), 2-[-(2-Phenyl-quinazolin-4-yl)-piperazin-1-yl]-ethylamine (250mg, 0.7mmol), prepared as in Intermediate 64, are added to a stirred solution of dimethylformamide (5 mL). After 2 h, the reaction is diluted with saturated sodium bicarbonate solution and chloroform. The aqueous layer is washed with chloroform and the organic layers are combined, dried with sodium sulfate, filtered and concentrated. The residue is purified by reverse phase HPLC using an eluant of acetonitrile : water (5% to 40% over 30 min) to give the title compound (0.33 g): ^{1}H NMR (CD_3OD) δ 8.36 (d, 2H J = 8 Hz), 8.23 (d, 1H, J = 8 Hz), 8.08-8.02 (m, 2H), 7.78-7.70 (m, 2H), 7.64 (t, 2H, J = 7 Hz), 4.56 (s, 4H), 4.36-4.33 (m, 1H), 3.99-3.96 (m, 1H), 3.89-3.84 (m, 1H), 3.79-3.73 (m, 1H), 3.33 (t, 2H, J = 6 Hz), 2.37-2.29 (m, 1H), 1.99-1.87 (m, 4H);
FAB MS m/z found 432. (MH^+).
Anal. Calcd. for $C_{25}H_{29}N_5O_2 \cdot 1.5\ H_2O \cdot 2\ C_2HF_3O_2$: C, 50.73; H, 4.99; N, 10.20.
Found: C, 51.07, H, 4.73; N, 9.91.

Example 79

4-[4-(3,3-Diphenyl-propyl)-piperazin-1-yl]-2-phenyl-quinazoline

2-Chloro-4-phenyl quinazoline(1.51 g, 5.37 mmol) was taken up in THF (18 mL) and to this solution was added Et_3N (1.1 mL, 8.05 mmol) and 1-(3,3-diphenyl-propyl)-piperazine (1.51 g, 5.37 mmol,Regnier, G.L *et al, J. Med Chem.* (1972), 15, 295-301). The solution was stirred for 16 h at ambient temperature then diluted with ethyl acetate (100 mL) and washed with H_2O (2 x 25 mL) and brine (1 x 25 mL). The

organic phase was dried with Na_2SO_4, filtered and the volatiles concentrated to give an oil which solidified upon standing. The white solid was collected and washed with ether to give the title compound (1.88 g):
^1H NMR (300 MHz, $CDCl_3$) δ 8.58 (m, 2H), 8.00 (d, 1H, J = 7.8 Hz), 7.9 (d, 1H, J = 8.1 Hz), 7.75 (t, 1H, J = 7.1 Hz), 7.53 (m, 3H), 7.43 (m, 1H), 7.33 (m, 7H), 7.22 (m, 3H), 4.10 (t, 1H, J = 7.4 Hz), 3.93 (m, 4H), 2.70 (m, 4H), 2.38 (m, 4H);
Anal. Calcd. for $C_{33}H_{32}N_4$: C, 81.8; H, 6.65; N, 11.56. Found: C, 81.3; H, 6.79 N, 11.75.

Example 80

4-[4-(2-Naphthalen-1-yl-ethyl)-piperazin-1-yl]-2-phenyl-quinazoline

2-Bromo-(1-naphthyl)ethane (3.30 g, 15.6 mmol) was mixed with 2-phenyl-4-piperazin-1-yl-quinazoline (3.8 g, 13.0 mmol) in CH_3CN (43 mL) with sodium iodide (1.95 g, 13.0 mmol) and N,N-diisopropylethyl amine (3.4 mL, 19.5 mmol) and heated to reflux for 22 h. The solution was cooled to room temperature and a solid precipitated. The solid was collected by vacuum filtration and washed with water then several portions of ether. The solid was recrystallized in hexanes:ether to provide the title compound (2.19 g) as a tan solid. Concentration and cooling of the filtrate provided additional compound (2.03 g, 35 %):
^1H NMR (400 mHz, $CDCl_3$) δ 8.57 (m, 2H), 8.08 (d, 1H, 8.2 Hz), 7.97 (d, 1H, J = 8.3 Hz), 7.91 (d, 1H, J = 8.2 Hz), 7.85 (d, 1H, J = 8.0 Hz), 7.72 (m, 2H), 7.53-7.39 (m, 8H), 3.95 (m, 4H), 3.34 (m, 2H), 2.84 (m, 6H);
Anal. Calcd for $C_{30}H_{29}N_4$: C, 6.6; H, 6.65; N, 12.6 Found: C, 80.9; H, 6.4 N, 12.6.

Example 81

2-(2-methoxy-5-{2-[4-(2-phenyl-quinazolin-4-yl)-piperazin-1-yl]ethyl}-benzenesulfonylamino)-acetamide

2-[5-(2-Chloro-ethyl)-2-methoxy-benzenesulfonylamino]-acetamide (1.6 g, 5.18 mmol), prepared as in Intermediate 65, was dissolved in dioxane (11.5 mL), and to this solution was added sodium iodide (0.52 g, 5.18 mmol), N,N-diisopropylethylamine (1.2 mL, 6.9 mmol) and 2-phenyl-4-piperazin-1-yl-quinazoline (1.00 g, 3.45 mmol). The solution was heated to 70 °C for 18.5 h then cooled to room temperature. The cooled solution was diluted with ethyl acetate (50 mL), washed with water (2 x 15 mL) and brine (1 x 20 mL). The organic phase was dried (Na_2SO_4), filtered and the volatiles concentrated to a brown oil. The residue was purified by silica gel flash column chromatography using methanol:ethyl acetate (1:20) containing 1% ammonium hydroxide as eluant to provide the title compound (1.47 g, 51%) as a light tan foam:
^1H NMR (400 MHz, DMSO-d_6) δ 8.46 (m, 2H), 7.89 (d, 1H, J = 8.2 Hz), 7.85, (d, 1H, J = 8.2 Hz), 7.78 (t, 1H, J = 7.6 Hz), 7.59 (m, 1H), 7.48 (m, 4H), 7.18 (bs, 2H), 7.12 (m, 3H), 3.81 (bs, 4H), 3.38 (d, 2H, J = 5.8 Hz), 2.77 (t, 2H, J = 7.5 Hz), 2.67 (bt, 4H), 2.56 (t, 2H, J = 7.5 Hz);
Anal. Calcd for $C_{29}H_{32}N_6O_4S$: C,62.13 ; H, 5.75 N, 14.99 Found: C, 62.20; H, 5.82; N, 15.01

Example 82

4-(4-Benzyl-piperazin-1-yl)-2-phenyl-quinazoline

2-Chloro-2-phenyl quinazoline (41.62 g, 173 mmol) was dissolved in tetrahydrofuran (350 mL) and to this solution was added triethylamine (48 mL, 346 mmol) then N-benzylpiperazine (33 mL, 190 mmol)(Lancaster) and the solution was heated to 70 °C for 2 h. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate:hexanes 1:1 (500 mL) and washed with water (3 x 100 mL) and brine (1 x 100 mL). The organics were dried (Na_2SO_4) filtered and the volatiles concentrated to yield a white solid. The solid was triturated with ether and filtered to provide the title compound (61.1 g):
Rf = 0.56 (1:3 ethyl acetate in hexanes);

^{1}H NMR (300 MHz, DMSO-d_6) δ 8.45 (m, 2H), 7.96 (d, 1H, J = 7.8 Hz), 7.87-7.78 (m, 2H,), 7.47 (m, 4H), 7.54 (m, 3H), 7.26 (m, 2H), 3.80 (bs, 4H), 3.54 (s, 2H), 2.60 (bs, 4H).

Example 83

{1-Methyl-5-[4-(2-phenyl-quinazolin-4-yl)-piperazin-1-yl-methyl]-1H-pyrrol-2-yl}-acetic acid methyl ester

2-Phenyl-4-piperazin-1-yl-quinazoline (5.03 g, 17.3 mmol), prepared as in Intermediate 66, was dissolved in MeOH (35 mL) then glacial acetic acid (1.1 mL, 18.2 mmol) was added and the mixture became very thick. Formaldehyde (37% in water, 2.1 mL) was added to the cooled (0 °C) slurry with stirring for 5 min. the cold bath was removed and the slurry was allowed to sit at ambient temperature for 5 min then methyl-1-methyl-2-pyrrole acetic acid was added with stirring continued for 3 h. The reaction mixture was poured into a saturated solution of Na_2CO_3 (100 mL) and extracted with methylene chloride (3 x 50 mL). The combined organic extracts were dried (Na_2SO_4) filtered and concentrated to a golden oil. The oil was purified by silica gel flash column chromatography with ethyl acetate:hexanes (3:7) as the eluant to furnish a slightly yellow oil which formed a white solid upon standing. The solid was crushed with mortar and pestle, and washed with ether to give the title compound (4.89 g):

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.41 (m, 2H), 7.83 (d, 1H, 8.6 Hz), 7.74 (d, 1H, 8.3 Hz), 7.58 (t, 1H, J = 8.0 Hz), 7.33 (m, 4H), 5.84 (m, 2H), 3.71 (bs, 4H), 3.58 (s, 3H), 3.51 (s, 2H), 3.47 (s, 3H), 3.39 (s, 2H), 2.52 (bs, 4H);

Anal. Calcd for $C_{27}H_{29}N_5O_2$: C, 1.06; H, 6.43; N, 15.36. Found: C, 71.18; H, 6.41; N, 15.32

Example 84

N-Methyl-2-{1-methyl-5-[4-(2-phenyl-quinazolin-4-yl)-piperazin-1-yl-methyl]-1H-pyrrol-2-yl}acetamide

{1-Methyl-5-[4-(2-phenyl-quinazolin-4-yl)-piperazin-1-yl-methyl]-1H-pyrrol-2-yl}-acetic acid methyl ester (1.07 g, 2.35 mmol), prepared as in Example 83, was dissolved in ethanol (12 mL) and placed in a sealed tube. A solution of methylamine in ethanol (3 mL, 8.03 M) was added and the tube sealed and heated to 70 °C for 20 h (CAUTION: pressure generated, use behind blast shield). After cooling to room temperature the contents of the tube were concentrated to a yellow oil, which solidified upon sitting. The solid was triturated with ether then recrystallized with ethyl acetate to furnish the title compound (0.95g);

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.45 (m, 2H), 7.98 (d, 1H), 7.85 (d, 1H, J = 8.2 Hz), 7.83 (t, 1H, J = 8.0 Hz), 7.73 (m, 2H), 7.47 (m, 4H), 5.80 (d, 1H, J = 3.4 Hz), 5.73 (d, 1H, J = 3.4 Hz), 3.78 (bs, 4H), 3.50 (s, 2H), 3.42 (s, 2H), 3.37 (s, 2H), 3.30 (s, 3H), 2.55 (m, 6H);

Reverse phase HPLC using acetonitrile:water (5% to 40% gradient over 30 min) as eluant t_r = 17.6 min;

FAB MS *m/z* found 455.3 (MH^+).

Example 85

N-(3-(1-hydroxy-2-[4-(2-phenyl-quinazoline-4-yl)-piperazin-1-yl]-ethyl)-phenyl)-methansulfonamide bis-maleic acid salt

To a dimethylformamide solution (60 mL) of N-[3-(2-bromo-acetyl)-phenyl]-methanesulfonamide (3.47 g, 12.02 mmol, Temple, D.L. *et al, J. Med. Chem.* (1976), 19(5) 626-33) was added N,N-diisopropylethyl amine (3.1 mL, 18 mmol) and 2-phenyl-4-piperazin-1-yl-quinazoline. The resultant solution was stirred at ambient temperature for 2 days. The solution was then diluted with ethyl acetate (100 mL) and washed with water (5 x 15 mL), dried (Na_2SO_4), filtered and concentrated. The resultant dark oil was dissolved in ethanol (60 mL) and sodium borohydride (1.8 g, 48.1 mmol) was added in 4 equal portions over 15 min at ambient temperature with stirring continued for 18 h. The reaction mixture was diluted with ethyl acetate (150 mL), and washed with water (3 x 20 mL), brine (1 x 50 mL) dried (Na_2SO_4), filtered and concentrated to a dark vicous oil. The oil was purified by silica gel flash column chromatography with ethyl acetate/hexanes (4:1) as the eluant to provide a light yellow viscous oil (3.44 g). The oil was dissolved in a minimum amount of ethanol and maleic acid (1.6 g, 13.7 mmol) was added as a solution in ethanol (3 mL). A solid was collected after 4 days and triturated with methanol and washed with ether to provide the title compound (3.052 g) as a white solid:
^{1}H NMR (400 MHz, DMSO-d_6) δ 9.83 (s, 1H), 8.48 (m, 2H), 8.06 (d, 1H, J = 8.4 Hz), 7.92 (d, 1H, J = 8.2 Hz), 7.86 (t, 1H, j = 7.5 Hz), 7.58-7.51 (m 4H), 7.33 (m, 3H), 7.11 (m, 2H), 7.11 (m, 2H), 6.36 (bs, 1H), 6.11 (s, 4H), 5.06 (d 1H, J = 9.7 Hz), 3.54 (bs, 4H), 3.29 (m, 2H), 2.97 (s, 4H);
Anal. Calcd for $C_{27}H_{29}N_5O_3S \cdot C_8H_8O_8$:C, 57.14; H, 5.07; N, 9.52. Found: C, 56.81 H, 5.10; N, 9.35.

Example 86

2-Methoxy-5-{2-[4-(2-phenyl-quinazoline-4-yl)-piperazin-1-yl]-ethyl}-benzoic acid methyl ester

To a solution of 5-(2-bromo-acetyl)-2-methoxy-benzoic acid methyl ester (1.75 g, 6.08 mmol, Collin, D. *et al, J. Med. Chem., 13(4)*, 674-80 (1970)) in methylene chloride (2 mL) was added trifluoroacetic acid (9.4 mL, 121 mmol) and triethylsilylhydride (9.7 mL, 60.8 mmol) and the mixture was stirred at ambient temperature for 2 h. The mixture was cautiously poured into a saturated solution of $NaHCO_3$, and extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated to furnish 5-(2-bromo-ethyl)-2-methoxy-benzoic acid methyl ester as an oil. which was used without further purification. To a solution of 2-phenyl-4-piperazin-1-yl-quinazoline (1.22 g ,4.21 mmol) in dioxane (14 mL) was added the 5-(2-bromo-ethyl)-2-methoxy-benzoic acid methyl ester (1.66 g, 6.08 mmol), N,N-diisopropylethylamine (1.5 mL, 8.42 mmol) and sodium iodide (0.631 g, 4.21 mmol). The mixture was heated to 91 °C for 22.5 h then cooled to room temperature, and partitioned between water and ethyl acetate. The phases were separated and the organic phase washed with water (2 x 25 mL), brine (1 x 50 mL), dried (Na_2SO_4), filtered and concentrated to a light brown oil. The oil was purified by silica gel flash column chromatography using ethyl acetate:hexanes (1:1) containing 1% ammonium hydroxide as eluant to furnish the title compound as a light orange oil (0.411 g). A portion of the oil (0.322 g, 0.667 mmol) was taken up in 3 mL of hot ethanol and to this was added maleic acid (0.75 g, 1.34 mmol) dissolved in a minimum amount of ethanol. A white solid formed and was filtered then washed with ethanol and ether to provide 2-methoxy-4-{2-[4-(2-phenyl-quinazoline-4-yl)-piperazin-1-yl]-ethyl}-benzoic acid methyl ester bis-maleic acid (0.305 g):

^1H NMR (300 MHz, DMSO-d_6) δ8.50 (m, 2H), 8.08 (d, 1H, J = 8.1 Hz), 7.96-7.87 (m, 2H), 7.58 (m, 2H), 7.53 (m, 3H), 7.45 (dd, 1H, J = 9.5, 2.4 Hz), 7.12 (d, 1H, J = 8.8 Hz), 6.13 (s, 4H), 3.79 (s, 3H), 3.77 (s, 3H), 3.60-3.45 (m, 2H), 3.37 (m, 2H), 2.99 (m, 2H), 2.48 (m, 6H);

Anal. Calcd for $C_{29}H_{30}N_4O_3 \cdot C_8H_8O_8$: C, 62.18; H, 5.36 N, 7.84 Found: C, 61.92; H, 5.52 N, 9.90.

Example 87

2-Methoxy-N-methyl-5-{2-[4-(2-phenyl-quinazolin-4-yl)-piperazin-1-yl]-ethyl}-benzamide bis-maleic acid salt

Synthesized in a manner similar to Example 84, using 2-Methoxy-5-{2-[4-(2-phenyl-quinazoline-4-yl)-piperazin-1-yl]-ethyl}-benzoic acid methyl ester (0.842 g, 1.74 mmol), prepared as in Example 86, to provide the title compound (127 mg): ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.65 (m, 2H), 8.27 (d, 1H, J = 4.6 Hz), 8.23 (d, 1H, J = 8.3 Hz), 8.10-7.99(m, 2H), 7.87 (d, 1H, J = 1.9 Hz), 7.74-7.66 (m, 4H), 7.50 (dd, 1H, J = 8.3, 1.9 Hz), 7.25 (d, 1H, J = 8.5 Hz), 6.28 (s, 1H), 4.00 (s, 3H), 3.67 (bs, 4H), 3.53 (m, 2H), 3.14 (m, 2H), 2.92 (m, 2H), 2.63 (s, 5H);
Reverse phase HPLC using acetonitrile:water (5% to 40% gradient over 30 min) as eluant t_r = 19.2 min;
Analysis Calcd. for $C_{29}H_{31}N_5O_2 \cdot C_8H_8O_8 \cdot 0.5\ H_2O$: C, 61.58; H, 5.58; N, 9.68.
Found: C, 61.92; H, 5.52; N, 9.90.

Example 88

2-Methoxy-5--{2-[4-(2-phenyl-quinazolin-4-yl)-piperazin-1-yl]-ethyl}-benzamide bis-maleic acid salt

2-Methoxy-5-{2-[4-(2-phenyl-quinazoline-4-yl)-piperazin-1-yl]-ethyl}-benzoic acid methyl ester (0.866 g, 1.80 mmol), prepared as in Example 86, was dissolved in ethanol (3.5 mL) and placed in a sealed tube. A solution of concentrated ammonium hydroxide (10 mL) was added and the tube sealed and heated to 70 °C for 21 h (CAUTION: pressure generated, use behind blast shield). After cooling to room temperature a small amount of precipitate began forming. Filtration of the solid and washing with water then ether caused the product to oil out. Ethyl acetate was added to the filtrate and stirred overnight. The precipitate that formed was collected and washed with ethyl acetate to furnish a slightly yellow solid (702 mg). The solid was dissolved in a minimum amount of warm ethanol and to this solution was added maleic acid (357 mg, 3.0 mmol) dissolved in a minimum amount of warm ethanol. After cooling to ambient temperature a white precipitate formed and collected and

washed with several portions of ethanol then ether to furnish the title compound (351 mg);
^{1}H NMR (400 MHz, CD_3OD) δ 8.43 (m, 2H), 8.12 (d, 1H, J = 8.3 Hz), 8.00 (d, 1H, J = 8.4 Hz), 7.91 (m, 2H), 7.64 (t, 1H, 7.4 Hz), 7.54 (m, 3H), 7.47 (dd, 1H, J = 8.5, 2.4 Hz), 7.13 (d, 1H, 8.6 Hz), 6.25 (s, 4H), 4.27 (bs, 4H), 3.96 (s, 3H), 3.60 (m, 4H), 3.42 (m, 2H), 3.11 (m, 2H);
Anal.Calcd. for $C_{28}H_{29}N_5O_2 \cdot C_8H_8O_8$ C, 61.80; H, 5.33; N, 10.18: Found; C, 61.50; H, 5.4; N, 9.8.

Example 89

4-{2-[4-(2-Phenyl-quinazolin-4-yl)-piperazin-1-yl]-ethyl}benzamide

To a solution of 2-phenyl-4-piperazin-1-yl-quinazoline (1.06 g, 3.65 mmol) in dioxane (18 mL) was added 4-(2-chloro-ethyl)-benzamide (1.0 g, 5.5 mmol), prepared as in Intermediate 67, N, N-diisopropylethylamine (1.9 mL, 10.8 mmol), and sodium iodide (0.56 g, 3.65 mmol). The mixture was heated to reflux for 22 h. After cooling to room temperature the mixture was diluted with ethyl acetate (50 mL) and washed with water (2 x 25 mL) and brine (25 mL), dried (Na_2SO_4) , filtered and concentrated to yield an orange oil. Addition of ether to the oil produced a white solid which was collected and washed with ether then triturated with hot methanol to provide the title compound (1.29 g):
^{1}H NMR (300 MHz, DMSO-d_6) δ 8.41 (m, 2H), 7.93-7.71 (m, 6H), 7.42 (m, 4H), 7.23 (m, 3H), 3.75 (bs, 4H), 2.76 (t, 2H, J = 7.8 Hz), 2.61-2.42 (m, 6H);
Reverse phase HPLC using acetonitrile:water (5% to 40% gradient over 30 min) as eluant t_r = 19.7 min; FAB MS *m/z* found 438.2 (MH^+).

Example 90

4-{4-[4,4-Bis-(4-fluoro-phenyl)-butyl]-piperazin-1-yl}-2-phenyl-quinazoline

To a tetrahydrofuran solution (17 mL) of 2-chloro-4-phenyl quinazoline (1.24 g, 5.15 mmol) was added triethylamine (2.2 mL, 15.5 mmol) and 1-[4,4-bis(4-fluoro-

phenyl)butyl]piperazine (1.7 g, 5.15 mmol)(Janssen). The reaction mixture was stirred at room temperature for 21 h.Thin layer chromatography (silica gel) with ethyl acetate:hexanes (3:1) containing 1% NH_4OH as eluant revealed the presence 2-chloro-4-phenyl quinazoline so additional 1-[4,4-bis(4-fluoro-phenyl)butyl]piperazine (450 mg, 1.4 mmol) was added with stirring continued at room temperature for 2h. The reaction mixture was diluted with ethyl acetate (50 mL) washed with water (2 x 20 mL), brine (1 x 20 mL), dried (Na_2SO_4) filtered and concentrated to a viscous yellow oil. The oil was purified by silica gel flash column chromatography using ethyl acetate: hexanes (1:3) containing 1% ammonium hydroxide as eluant to furnish the title compound (2.87 g) as a slightly yellow oil; Reverse phase HPLC using acetonitrile:water (5% to 40% gradient over 30 min) with 1% trifluoroacetic acid as eluant t_r = 33.1 min;

^1H NMR (300 MHz, DMSO-d_6) δ 8.40 (m, 2H), 7.89 (d, 1H, 8.0 Hz), 7.88-7.70 (m, 2H), 7.41 (m, 4H), 7.25 (dd, 4H, J = 8.5, 5.6 Hz), 7.02 (t, 4H, J = 9.0 Hz), 3.93 (m, 1H), 3.71 (bs, 2H), 3.26 (s, 2H), 2.42 (bs, 4H), 2.27 (t, 2H, J = 6.8 Hz), 1.93 (m, 2 H), 1.27 (m, 2H);

FAB MS *m/z* found 535 (MH^+).

Example 91

5-[1-hydroxy-2-[4-(2-Phenyl-quinazolin-4-yl)-piperazin-1-yl]-2-methoxy-benzamide

To a solution of 2-phenyl-4-piperazin-1-yl-quinazoline (1.67 g, 5.75 mmol) in dimethylformamide (19.2 mL) was added N,N-diisopropylamine (2 mL, 11.5 mmol) and 5-(2-bromo-acetyl)-2-methoxy-benzoic acid methyl ester (1.65 g, 5.75 mmol, Collin, David T. *et al, J. Med. Chem.* (1970), 13(4), 674-80)). After 36 h the reaction mixture was diluted with ethyl acetate and washed with water (4 x 20 mL) then brine (25 mL), dried (Na_2SO_4), filtered and concentrated to red viscous oil, which was used without further purification. The red oil was taken up in ethanol (30 mL) and to this solution was added sodium borohydride (87 mg, 23 mmol) in two equal portions with stirring at ambient temperature for 16 h. The volatiles were concentrated then the residue was dissolved in ethyl acetate (75 mL) and washed with water (3 x 25 mL) and brine (25 mL), dried (Na_2SO_4), filtered and concentrated to a viscous burnt

orange oil. The oil was purified by silica gel flash column chromatography using methanol:methylene chloride (1:9) to furnish 1.27 g of a light yellow foam. This foam was dissolved in ethanol (8.7 mL) and placed in a sealed tube. A solution of methylamine in ethanol (8.03 M, 7.5 mL) was added and the tube sealed and heated to 70 °C for 14.75 h (CAUTION: pressure generated, use behind blast shield). After cooling to room temperature the contents of the tube were concentrated to a viscous yellow oil. The oil was purified by silica gel flash column chromatography using ethyl acetate: hexanes (3:1 to 9:1 to 100%, gradient elution) containing 1% ammonium hydroxide as eluant to furnish the title compound as a slightly yellow oil (0.577 g). Rf = 0.18 (3:1 ethyl acetate in hexanes);
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39 (m, 2H), 8.02 (d, 1H, J = 2.2 Hz), 7.83 (d, 1H, 8.1 Hz), 7.73 (d, 1H, 8.6 Hz), 7.70 (m, 1H), 7.58 (m, 1H), 7.40 (dd, 1H, J = 8.6, 2.5 Hz), 7.3 (m, 3H), 7.20 (m, 1H), 6.83 (d, 1H, 8.8 Hz), 5.52 bs, 3H), 4.72 (m, 1H), 3.86 (m, 5H), 2.85 (d, 2H, J = 4.7 Hz), 2.65 (m, 7H);
Reverse phase HPLC using acetonitrile:water (5% to 40% with 1% trifluoroacetic acid, gradient over 30 min) as eluant t_r = 18.3 min;
FAB MS *m/z* found 498.3 (MH^+).

Example 92

<u>4-(3-phenyl piperazin-1-yl)-2-phenyl-quinazoline</u>

A solution of 4-chloro-2-phenyl-quinazoline (2.00 g, 12.3 mmol) in THF (25 ml) was treated with 2-phenylpiperazine (2.0 g, 12.3 mmol)(Kitchen,P.; *J.Amer.Chem.Soc.,69* (1947) pg.854), and triethylamine (2.48 g,24.6 mmol), and heated to 70°C for 1.5 hr The mixture was cooled and concentrated. The residue was diluted with satur'd
Na_2CO_3 (20 ml) and extracted with ethyl acetate. The organic phases were combined and dried over $MgSO_4$, filtered and concentrated.The crude residue was purified by silica gel chromatography using 95:5 $CHCl_3$:MeOH to give the title compound as (900 mg):
^{1}H ($CDCl_3$) δ 8.78 (d, 2H),7.95 (m,2H),7.75 (t,1H), 7.21-7.61(m,9H), 4.45 (d,2H) 4.15 (dd,2H), 3.51 (m,2H), 3.29 (m,2H), 2.41 (b,1H):

FAB MS 367 (MH+).
Theory:$C_{24}H_{22}N_4$ C 78.66, H 6.05, N 15.28. Found:C 78.40, H 6.15, N 15.20.

Example 93

5-{2-[2-phenyl-4-(2-phenyl-quinazolin-4-yl)-piperazin-1-yl]-ethyl}-2-methoxy-benzenesulfonamide bistrifluoroacetate

A solution of potassium carbonate (677 mg,4.9 mmol), sodium iodide (734 mg, 4.9 mmol) in ethanol (5ml) was treated with N-(3-{1-hydroxy-2-[4-(2-phenyl-quinazoline-4-yl)-piperazin-1-yl]-ethyl}-phenyl)-methansulfonamide bis-maleic acid salt (900 mg, 2.45 mmol), prepared as in Example 85, dissolved in ethanol (16 ml) followed by the addition of 5-(2- chloro-ethyl)-2-methoxy-benzene-sulfonamide (1.22g,4.9 mmol) heated at 135 °C in a sealed tube for 6 hr.The mixture was cooled and concentrated. The residue was diluted with H_2O (50ml) and satur'd $NaHCO_3$ (50ml).The mixture was extracted with ethyl acetate.The organic extracts were combined and dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by silica gel chromatography using 80:20 ethyl acetate :hexane to obtain the product which was further purified by reverse phase HPLC using acetonitrile:water .1%TFA (15-85% gradient over 30min.) as eluent to give the title compound (65 mg):

^1H NMR (CD_3OD) δ 8.31(m,2H),8.05 (d,1H), 7.41-7.82 (m,12H), 7.13 (d,1H), 7.03 (d,1H), 5.12 (d,1H), 5.02(d,1H), 4.55 (d,1H), 4.27 (t,2H), 2.77-3.55 (m,3H):

FAB MS 580 (MH+).

Theory:$C_{33}H_{33}N_5O_3S:2C_2HF_3O_2$; C 52.66, H 4.65, N 8.30. Found C 52.21, H 4.37, N 7.91.

Example 94

2-(2-phenyl-quinazolin-4yl)-2,3,4,6,7,11b-hexahydro-1H-pyrazino [2,1-a]isoquinoline

A solution of 4-chloro-2-phenyl-quinazoline (2.16 g, 9.0mmol), in THF (60ml) was treated with 1,2,3,6,7,11b-hexahydro-4H-pyrazino[2,1-a]isoquinoline (850 mg, 4.5

mmol) (Belg.659,249,(1985)), and triethylamine (2.27 g, 22.5mmol) and heated at 65°C for 6hr. The mixture was cooled and concentrated.The crude residue was purified by silica gel chromatography using 60:40 hexane:ethyl acetate to obtain the desired material which was converted into the maleic acid salt. The compound was dissolved in hot ethanol then treated with 2 equiv. maleic acid. Solvent was concentrated and the residue left was recrystallized from ethyl acetate to give the title compound (125 mg,):[1]

H (d6 DMSO) δ 8.58 (d,2H), 8.0 (t,2H), 7.78 (t,1H), 7.50 (m,4H), 7.13-7.25 (m,4H), 5.05 (d,1H), 4.45 (d,1H), 2.61-3.79 (m,8H):

FAB MS 393 (MH+).

Theory $C_{26}H_{24}N_4.1/4H_2O$ C 69.62 H 5.64 N 10.82. Found

Example 95

5-{2-[2,2-dimethyl-4-(2-phenyl-quinazolin-4-yl)-piperazin-1-yl}-ethyl}-2-methoxy-benzenesulfonamide dimaleate sesquihydrate

A solution of 4-(3,3-Dimethyl-piperazine-1-yl)-2-phenyl-quinazoline (1.40 g,4.39 mmol), prepared as in Intermediate 68, 5-(2-chloro-ethyl)-2-methoxy-benzene-sulfonamide (2.19 g,8.78 mmol),potassium carbonate (1.21 g,8.78 mmol), and sodium iodide (678 mg,4.39 mmol) in dry acetonitrile (60ml) was heated and stirred at 80 C for 6 hr. The reaction mixture was cooled and solids were removed by filtration.The filtrate was concentrated and the residue diluted with satur'd $NaHCO_3$ and extracted with ethyl acetate (4X25 mls).The organic phases were combined and dried over $MgSO_4$, filtered and concentrated to give crude product which was purified by silica gel chromatography using 70:30 hexane:ethyl acetate to obtain the desired material. The compound was dissolved in hot ethanol then treated with 2 equiv. maleic acid. The solvent was concentrated and the residue was crystallized from ethyl acetate to give the title compound (425 mg):

^1H NMR ($CDCl_3$) δ 8.63 (d,1H), 7.91 (m,1H),7.80 (s,1H), 7.75 (t,1H), 7.33-7.45(m,5H), 6.98 (d,1H), 5.0 (s,2H), 4.0 (s,3H),3.85 (m,1H), 3.56 (m,1H), 2.61-2.82 (m,3H), 1.57 (bs,1H), 1.02 (s,6H):

FAB MS 532 (MH+).

$C_{29}H_{33}N_5O_3S$. $2C_4H_4O_4$.11/2 H_20 C 56.19, H 5.61, N 8.86.
Found C 56.09, H 5.56, N 7.99.

Example 96

5-[2-[1-(2-Phenyl-quinazolin-4yl)-piperidin-1-ylamino]-methyl]-2-methoxy-benzenesulfonamide bistrifluoroacetate dihydrate

A solution of 4-Methoxy-3-(aminosulfonyl)benzaldehyde (592 mg,2.75 mmol) (Kruse,L., *et al, J.Med.Chem., 30, No.3,* 492 (1987)), and 1-(2-phenyl-quinazolin-4-yl)-piperadin-4-yl-amine (2.0 g,4.78 mmol), prepared as in Intermediate 2, was dissolved in 1,2-dichloroethane (25ml) and cooled to O°C.To the cooled solution was added glacial acetic acid (165mg,2.75 mmol).The mixture was stirred for 30 min. at 0°C then added sodium triacetoxyborohydride (1.16 g,5.5 mmol) and the ice bath removed. The reaction mixture pH 6 was stirred at rt for 16hr.The mixture was diluted with H_2O (25ml) and solid $NaHCO_3$ was added to pH 7. The aqueous layer was extracted with CH_2Cl_2 (3X50ml).The organic phases were combined and dried over $MgSO_4$,filtered and concentrated to give crude which was purified by silica gel chromatography using 9:1 CH_2Cl_2:MeOH to obtain the desired product which was further purified by reverse phase HPLC using acetonitrile:water.1%TFA 15-85% gradient over 30 min.) as eluent to give the title compound (600 mg):
^1H (d6 DMSO) δ 8.97 (bs,2H), 8.42 (d,2H), 8.05 (d,1H), 7.91 (m,2H),7.61 (m,4H), 7.26 (d,1H), 7.11 (s,1H), 4.65 (m,2H), 4.25 (bs,2H),
3.89 (s,3H),3.49 (m,3H), 2.25 (d,2H), 1.87 (q,2H):
FAB MS 504 (MH+).
$C_{27}H_{29}N_5O_3S$.$2C_2HF_3O_2$.$2H_2O$ C 48.50 H 4.60 N 9.12 Found: C 48.24 H 4.28 N 8.80.

Example 97

2-Methoxy-5-[2-[8-(2-phenyl-quinazolin-4-yl)-3,8-diaza-bicyclo[3.2.1]oct-3-yl]-ethyl]-benzenesulfonamide bistrifluoroacetate monohydrate

A solution of 4-(3,8-diaza-bicyclo[3.2.1.]oct-8-yl)-2-phenyl-quinazoline (200 mg,.63 mmol), prepared as in Intermediate 69, 5-(2-chloro-ethyl)-2-methoxy-benzene-sulfonamide (314 mg, 1.26 mmol), potassium carbonate (174 mg, 1.26 mmol), and sodium iodide (95mg,.63 mmol), in dry acetonitrile (25 ml)was heated at reflux for 12 hr.The reaction was cooled and solids were removed by filtration. The filtrate was concentrated and the residue diluted with satur'd $NaHCO_3$ and extracted with ethyl acetate (4X25mls).The organic phases were combined and dried over $MgSO_4$, filtered and concentrated to give crude title compound which was purified by silica gel chromatography using 1:1 hexane:ethyl acetate, which was further purified by reverse phase HPLC using acetonitrile:water.1% TFA (15-85% gradient over 30 min.) as eluent to give the title compound (78 mg):

^1H (CDCl3) δ 8.53 (d,2H), 7.92 (m,2H), 7.7 (m,2H), 7.42 (m,4H), 6.98 (t,2H), 5.08 (s,2H),4.91 (s,2H), 3.97 (s,3H),2.61-2.95 (m,4H), 0.89 (bs,2H):

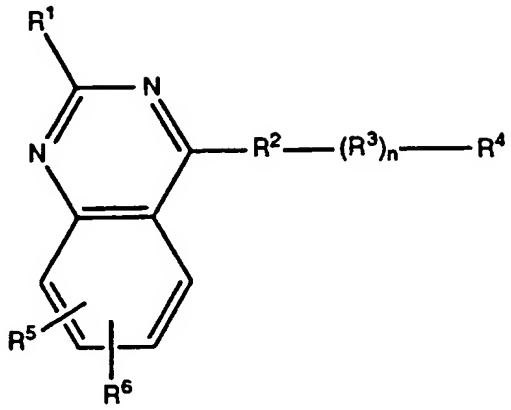
FAB MS 530 (MH+). $C_{29}H_{31}N_5O_3S \cdot 2C_2HF_3O_2 \cdot 1H_2O$

C 49.07, H 4.37, N 8.67. Found: C 49.02, H 4.37, N 8.31.

What is claimed is:

1. Quinazoline compounds of the following formula (I):

(I)



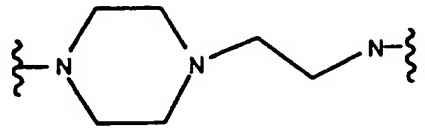
wherein:

R^1 is selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{1-6}cycloalkyl, hydroxy, C_{1-6}alkoxy, -COO(C_{1-6}alkyl), halogen, phenyl, phenylcarbonyl, substituted phenyl, pyridinyl, pyrimidinyl or pyrrolyl;

R^2 is selected from the group consisting of

(a) NH,

(b)



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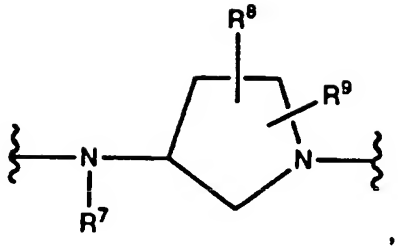

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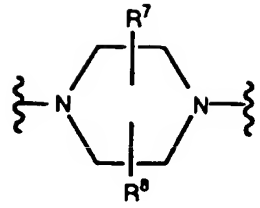

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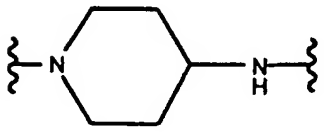

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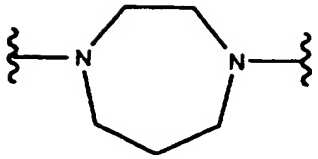

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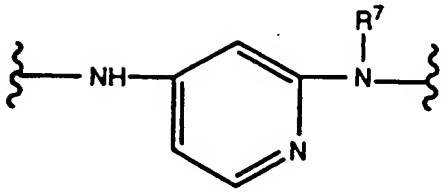
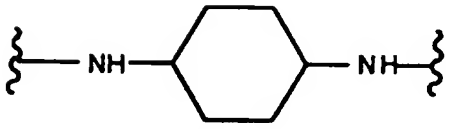


(h)



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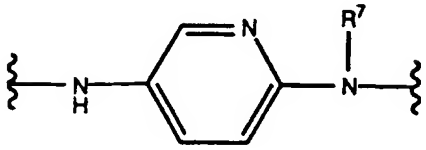
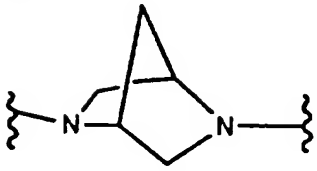


(j) $-N(CH_2)_mNR^7-$,

(k)



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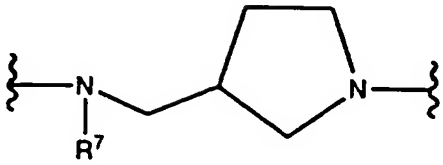
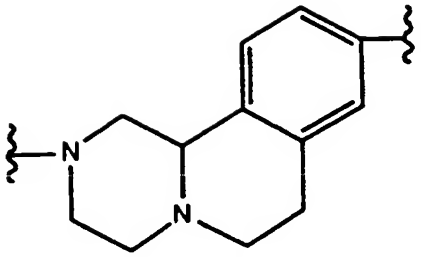
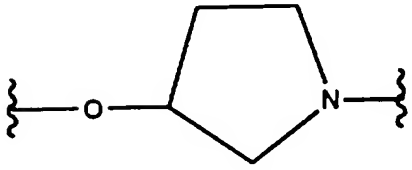


(m)



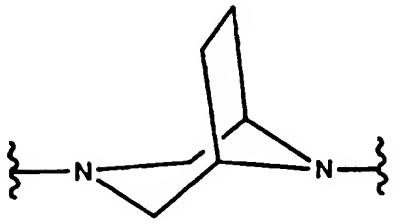
(n) $-(CH_2)_mNR^7-$,

(o)



(p) $-SO(CH_2)_mNR^7-$,

(q)



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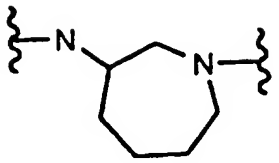

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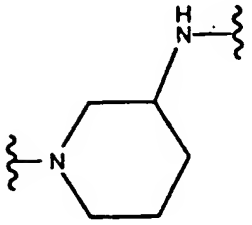
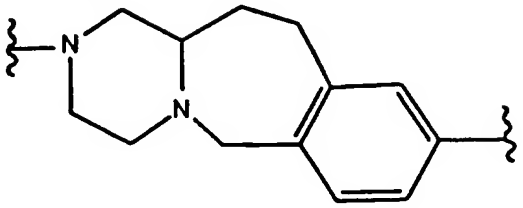


(t)



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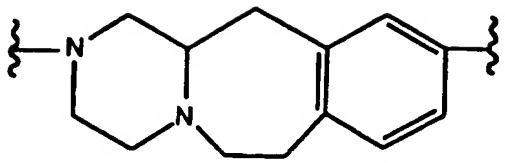
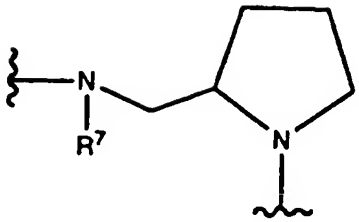
(u)



(v)



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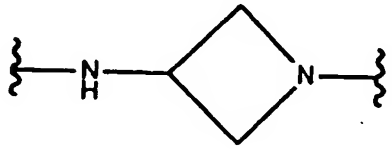

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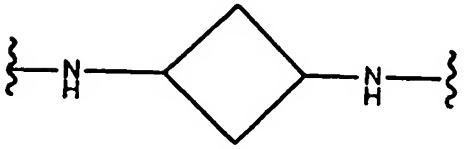
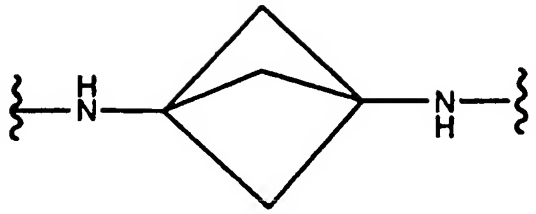


(y)



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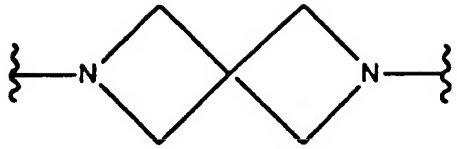

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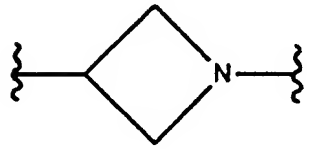

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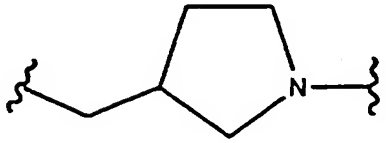

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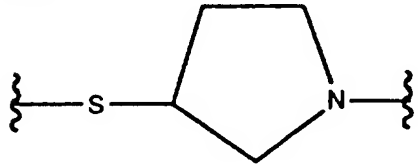

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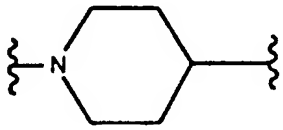

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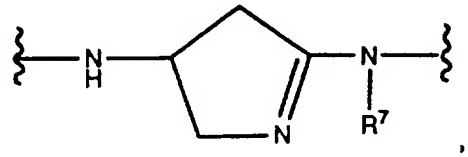

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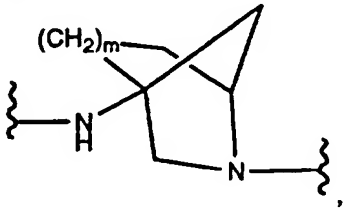

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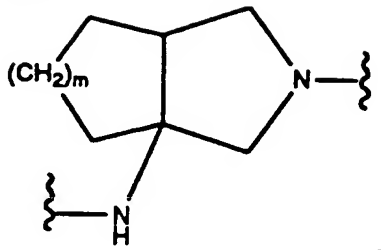
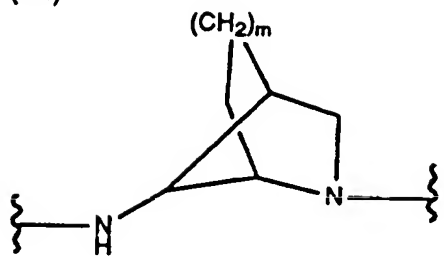
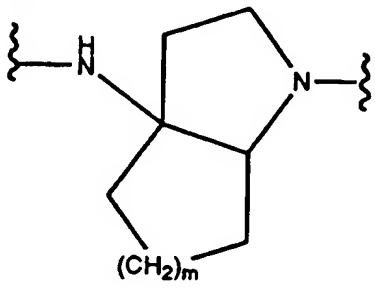


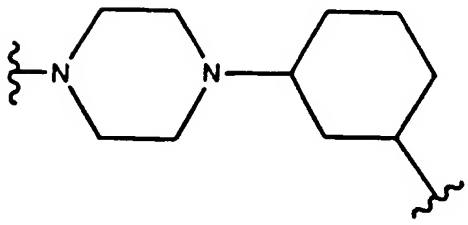
(hh)



(ii)



(jj)



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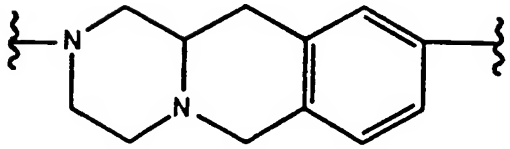
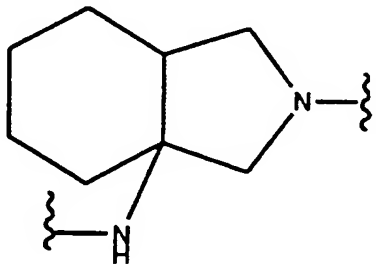
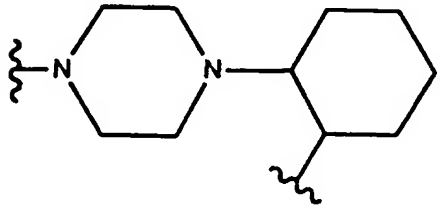


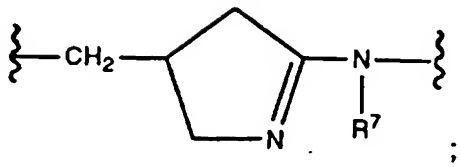
(ll)



(mm)



or (nn)



wherein:

R^7, R^8 and R^9 are selected from hydrogen, C_{1-6}alkyl, phenyl or benzyl;

m is an integer selected from the group consisting of 0, 1, 2, 3, 4, 5 or 6;

n is an integer selected from the group consisting of 0 or 1;

R^3 is a C_{1-6}alkylene chain optionally mono- or disubstituted independently with hydrogen, C_{1-6}alkyl, hydroxy, C_{1-6}alkoxy, fluoro, phenyl or substituted phenyl substituents;

R^4 is selected from the group consisting of hydrogen, amino, mono- or di(C_{1-6}alkyl)amino, phenyl, substituted phenyl, phenyloxy, (substituted phenyl)oxy, pyrrolyl, pyrrolyl mono- or disubstituted independently with C_{1-8}alkyl, -C_{1-6}alkylCOO(C_{1-4}alkyl) or C_{1-6}alkylcarbamylC_{1-6}alkyl substituents, C_{1-8}alkylcarbonylamino, 5 or 6 membered saturated heterocycle, (5 or 6 membered saturated heterocycle)carbonylamino, substituted 5 or 6 membered saturated heterocycle, (substituted 5 or 6 membered saturated heterocycle)C_{1-6}alkenyl, (substituted 5 or 6 membered saturated heterocycle)carbonyl, (substituted 5 or 6 membered saturated heterocycle)C_{1-6}alkylcarbonyl, quinoline, 9 or 10 membered heterobicycle which is partially aromatic, substituted 9 or 10 membered heterobicycle which is partially aromatic or (substituted 9 or 10 membered heterobicycle which is partially aromatic)carbonyl;

R^5 and R^6 are independently selected from the group consisting of hydrogen, C_{1-6}alkyl, hydroxy, C_{1-6}alkoxy or halogen;

substituted phenyl in more detail is phenyl mono-, di- or tri-substituted independently with C_{1-6}alkyl, C_{1-6}alkenyl, halo, nitro, amino, hydroxy, oxo, carboxy, C_{1-6}alkyl substituted with hydroxy, C_{1-6}alkoxy, C_{1-6}alkenyloxy, C_{1-6}alkenyloxyC_{1-6}alkyl, C_{1-6}alkylcarbonyl, C_{1-6}alkoxycarbonyl, C_{1-6}alkoxycarbonylamino, C_{1-6}alkoxycarbonylC_{1-6}alkoxy, biphenylcarbonylC_{1-6}alkoxy, napthylcarbonylC_{1-6}alkoxy, C_{1-6}alkoxycarbonylC_{1-6}alkyl, C_{1-6}alkoxycarbonylC_{1-6}alkylcarbonylamino, aminosulfonyl, sulfonylamino, C_{1-6}alkylsulfonylamino, C_{1-6}alkylcarbonylamino, C_{1-6}alkylaminosulfonyl, C_{1-6}alkylaminocarbonyl, aminoC_{1-6}alkylaminosulfonyl,

aminosulfonylC_{1-6}alkylaminosulfonyl, C_{1-6}alkylsulfonylaminoC_{1-6}alkyl, C_{1-6}alkylsulfonylaminoC_{1-6}alkylaminosulfonyl, C_{3-6}cycloalkylaminosulfonyl, mono- or di(C_{1-6}alkyl)amino, mono- or di(C_{1-6}alkyl)aminosulfonyl, mono- or di(C_{1-6}alkyl)aminocarbonylC_{1-6}alkoxy, heteroarylaminosulfonyl, dioxopyrimidinylaminosulfonyl, (C_{1-6}alkylcarbonyl)(C_{1-6}alkyl)aminosulfonyl, (C_{1-6}alkoxycarbonyl)(C_{1-6}alkyl)aminosulfonyl, C_{1-6}alkylcarbonylamino, C_{1-6}alkylcarbonylaminosulfonyl, C_{1-6}alkoxycarbonylC_{1-6}alkylaminosulfonyl, C_{1-6}alkylcarbonylaminoC_{1-6}alkylaminosulfonyl, fluorinated C_{1-6}alkyl, fluorinatedC_{1-6}alkylcarbonylaminoC_{1-6}alkylaminosulfonyl, fluorinatedC_{1-6}alkylsulfonate, fluorinatedC_{1-6}alkylsulfonylaminoC_{1-6}alkylaminosulfonyl, C_{1-6}alkylaminocarbonylamino, C_{1-6}alkylaminocarbonylaminoC_{1-6}alkylaminosulfonyl, C_{1-6}alkoxycarbonylaminoC_{1-6}alkylaminosulfonyl, C_{1-6}alkylcarbonyl(C_{1-6}alkyl)aminoC_{1-6}alkyl(C_{1-6}alkyl)aminosulfonyl, C_{1-4}alkylcarbonylsulfonylaminoC_{1-6}alkylaminosulfonyl, C_{1-6}alkylaminocarbonylC_{1-6}alkyl(C_{1-6}alkyl)aminosulfonyl, fluorinatedC_{1-4}alkylcarbonylsulfonylaminoC_{1-6}alkylaminosulfonyl, C_{1-6}alkylaminocarbonylC_{1-6}alkylaminosulfonyl, (C_{1-6}alkylaminocarbonyl)(C_{1-6}alkyl)methyleneaminosulfonyl, napthylaminocarbonylC_{1-6}alkylaminosulfonyl, C_{1-6}alkylaminocarbonylC_{1-8}alkylamino, C_{1-6}alkylaminocarbonylC_{1-8}alkylaminosulfonyl, mono- or di(C_{1-6}alkyl)aminocarbonylC_{1-8}alkylaminosulfonyl, mono- or di(C_{1-6}alkyl)aminocarbonylC_{1-6}alkyl(C_{1-6}alkyl)aminosulfonyl, phenyl, phenylC_{1-6}alkyl, phenylC_{1-6}alkoxy, phenylcarbonyl, phenylcarbonylamino, phenylC_{1-6}alkylcarbonyl, phenylC_{1-6}alkylcarbonylamino, phenylC_{1-6}alkylcarbonylaminosulfonyl, phenylC_{1-6}alkylcarbonylaminoC_{1-6}alkyl, phenylaminosulfonyl, phenylsulfonylaminoC_{1-6}alkyl, phenylcarbonylC_{1-6}alkoxy, phenylC_{1-6}alkylaminocarbonylaminosulfonyl, phenylcarbonylaminoC_{1-6}alkylaminosulfonyl, phenylcarbonylsulfonylaminoC_{1-6}alkylaminosulfonyl, phenoxy, halophenoxy, halophenylcarbonylC_{1-6}alkoxy, halophenylcarbonylamino, phenylC_{1-6}alkylaminosulfonyl, phenylaminocarbonylamino, phenylaminocarbonylaminosulfonyl, phenylC_{1-6}alkylaminocarbonylaminosulfonyl, phenylcarbonylaminosulfonyl, C_{1-6}alkylphenylcarbonylaminosulfonyl, phenylC_{1-6}alkoxycarbonylC_{1-6}alkyl, thiadiazolyl, 5, 6 or 7 membered saturated heterocycle, substituted 5, 6 or 7 membered saturated heterocycle, (5, 6 or 7 membered saturated heterocycle)carbonyl, (5, 6 or 7 membered saturated heterocycle)sulfonyl, (substituted 5, 6 or 7 membered saturated

heterocycle)C_{1-6}alkyl, (substituted 5, 6 or 7 membered saturated heterocycle)carbonyl, (substituted 5, 6 or 7 membered saturated heterocycle)sulfonyl, (substituted 5, 6 or 7 membered saturated heterocycle)aminosulfonyl, heteroaryl, heteroarylaminosulfonyl, substituted heteroaryl, (substituted heteroaryl)amino sulfonyl, carbamyl, carbamylamino, carbamylC_{1-6}alkylamino, carbamylC_{1-6}alkylaminosulfonyl, (carbamyl)(phenyl)methyleneaminosulfonyl, (carbamyl)(benzyl)methyleneaminosulfonyl, (carbamyl)(C_{1-6}alkyl)methyleneaminosulfonyl, carbamylC_{1-6}alkyl(C_{1-6}alkyl)aminosulfonyl, carbamylC_{1-8}alkylaminosulfonyl, carbamylaminoC_{1-6}alkylaminosulfonyl, carbamyl(5, 6 or 7 membered saturated heterocycle), azaindolylC_{1-6}alkylaminosulfonyl, cyano or carboxyC_{1-6}alkoxy substituents;

5, 6 or 7 membered saturated heterocycle in more detail is a 5, 6 or 7 membered saturated heterocycle interrupted by 1, 2, 3, or 4 N or O heteroatoms, with the proviso that any two O atoms are not bonded to each other;

substituted 5, 6 or 7 membered saturated heterocycle in more detail is a 5, 6 or 7 membered saturated heterocycle mono-, di-, or trisubstituted independently with hydroxy, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, carbamyl, acetyl, amino, C_{1-6}alkylsulfonyl, -COO(C_{1-4}alkyl), benzyl or C_{1-6}alkylcarbonyl substituents;

9 or 10 membered heterobicycle which is partially aromatic in more detail is a heterobicycle interrupted by 1, 2, 3, or 4 N heteroatoms,

substituted 9 or 10 membered heterobicycle which is partially aromatic in more detail is a 9 or 10 membered heterobicycle mono-, di-, or trisubstituted independently with hydroxy, oxo, C_{1-6}alkyl, C_{1-6}alkoxy or amino substituents;

heteroaryl in more detail is a 5, 6 or 7 membered aromatic ring optionally interrupted by 1, 2, 3 or 4 N, S, or O heteroatoms, with the proviso that any two O or S atoms are not bonded to each other;

substituted heteroaryl in more detail is a 9 or 10 membered heterobicycle mono-, di-, or trisubstituted independently with hydroxy, oxo, C_{1-6}alkyl, C_{1-6}alkoxy or amino substituents;

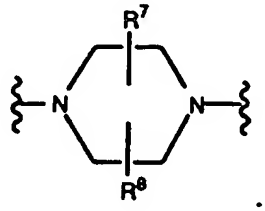
or a pharmaceutically acceptable acid-addition or base-addition salt thereof.

2. The Quinazoline compounds of Claim **1**, wherein:

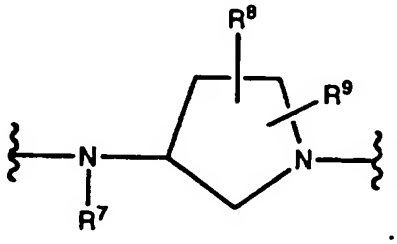
R^4 is phenyl disubstituted with methoxy and aminosulfonyl.

3. The Quinazoline compounds of Claim 1, wherein:
$R^4$is (3-aminosulfonyl-4-methoxy)phenyl.

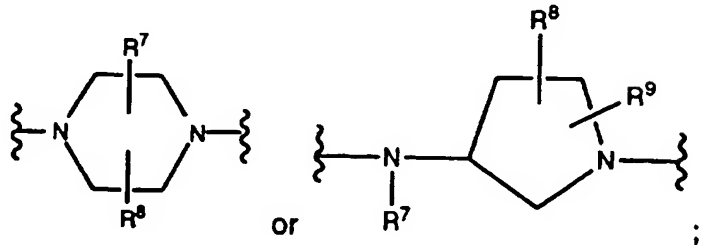
4. The Quinazoline compounds of Claim 1, wherein:
R^2 is



5. The Quinazoline compounds of Claim 1, wherein:
R^2 is



6. The Quinazoline compounds of Claim 1, wherein:
R1 is phenyl or phenyl mono-substituted with fluoro;
R^2 is



;

R^7 is hydrogen;
R^8 iand R^9 are hydrogen or methyl;
n is 1;

R^3 is ethylene;

R^4 is phenyl disubstituted with methoxy and aminosulfonyl.

7. The Quinazoline compounds of Claim 1, wherein:

R^1 is phenyl mono or disubstituted with fluorine.

8. Quinazoline compounds of Claim 1, wherein the quinazoline is selected from the group consisting of:

5-{2-[4-(2-Phenyl-quinazolin-4-yl)-[1,4]diazepan-1-yl]-ethyl}-2-methoxy-benzenesulfonamide bistrifluoroacetate

5-{2-[4-(2-Phenyl-quinazolin-4-ylamino)-piperidin-4-yl]-ethyl}-2-methoxy-benzenesulfonamide bistrifluoroacetate

5-{2-[2-Methyl-4-(2-phenyl-quinazolin-4-yl)-piperazin-1-yl]-ethyl}-2-methoxy-benzenesulfonamide bistrifluoroacetate

2-(2-Phenyl-quinazolin-4-yl)-1,2,3,4,6,7,12,12a-octahydro-benzo[4,5]azepino[1,2-a]pyrazine bistrifluoroacetate

2-(2-Phenyl-quinazolin-4-yl)-1,2,3,4,6,11,12,12a-octahydro-benzo[5,6]azepino[1,2-a]pyrazine bistrifluoroacetate

5-{2-[3-(2-Phenyl-quinazolin-4-ylamino)-piperidin-1-yl]-ethyl}-2-methoxy-benzenesulfonamide

5-{2-[3-(2-Phenyl-quinazolin-4-ylamino)-azepan-1-yl]-ethyl}-2-methoxy-benzenesulfonamide

5-{2-[3,5-Dimethyl-4-(2-phenyl-quinazolin-4-yl)-piperazin-1-yl]-ethyl}-2-methoxy-benzenesulfonamide trifluoroacetate

5-{2-[3-Methyl-4-(2-phenyl-quinazolin-4-yl)-piperazin-1-yl]-ethyl}-2-methoxy-benzenesulfonamide trifluoroacetate

5-{2-[1-(2-Phenyl-quinazolin-4-yl)-piperidin-1-ylamino]-ethyl}-2-methoxy-benzenesulfonamide trifluoroacetate

N 2-Benzyl-N 2-methyl-N 4-(2-Phenyl-quinazolin-4-yl)-pyridine-2,4-diamine trifluoroacetate

N 2-Benzyl-N 2-methyl-N 5-(2-Phenyl-quinazolin-4-yl)-pyridine-2,5-diamine

5-2-{Methyl-[3-(2-Phenyl-quinazolin-4-yl)-propyl]-amino}-ethyl)-2-methoxy-benzenesulfonamide trifluoroacetate

5-(2-{3-[Methyl-(2-phenyl-quinazolin-4-yl)-amino]-pyrrolidin-3-yl}-ethyl)-2-methoxy-benzenesulfonamide bistrifluoroacetate

5-{2-[3-Methyl-3-(2-phenyl-quinazolin-4-yl-amino)-pyrrolidin-1-yl]-ethyl}-2-methoxy-benzenesulfonamide bistrifluoroacetate

5-{2-[3,4-Dimethyl-3-(2-phenyl-quinazolin-4-yl-amino)-pyrrolidin-1-yl]-ethyl}-2-methoxy-benzenesulfonamide bistrifluoroacetate

5-{2-[2,5-dimethyl-4-(2-phenyl-quinazolin-4-yl)-piperazin-1-yl]-ethyl}-2-methoxy-benzenesulfonamide

2-Methoxy-5-{2-[4-(2-phenyl-quinazolin-4-ylamino)-cyclohexyl-amino]-ethyl}-benzenesulfonamide bistrifluoroacetate

(R)-2-methoxy-5-{2-[3-(2-phenyl-quinazolin-4-ylamino)-pyrrolidin-1-yl]-ethyl}-benzenesulfonamide

(R)-2-methoxy-5-{2-[1-(2-phenyl-quinazolin-4-yl)-pyrrolidin-3-ylamino]-ethyl}-benzenesulfonamide bistrifluoroacetate

(S)-2-Methoxy-5-{2-[3-(2-phenyl-quinazolin-4-ylamino)-pyrrolidin-1-yl]-ethyl}-benzenesulfonamide bistrifluoroacetate

(S)-N-Acetyl-2-methoxy-5-{2-[3-(2-phenyl-quinazolin-4-ylamino)-pyrrolidin-1-yl]-ethyl}-benzenesulfonamide bistrifluoroacetate

(S)-2-Hydroxy-5-{2-[3-(2-phenyl-quinazolin-4-ylmino)-pyrrolidin-1-yl]-ethyl}-benzenesulfonamide bistrifluoroacetate

(S)-2-methoxy-5-[2-[1-(2-phenyl-quinazolin-4-yl)-pyrrolidin-3-ylamino]-ethyl}-benzenesulfonamide bistrifluoroacetate

2-Methoxy-5-{2-[5-(2-phenyl-quinazolin-4-yl)-2,5-diazo-bicyclo[2.2.1]hept-2-yl]-ethyl}-benzenesulfonamide bistrifluoroacetate

2-Methoxy-5-(2-{methyl-[2-(2-phenyl-quinazolin-4-ylamino)-ethyl]-amino}-ethyl)-benzenesulfonamide bistrifluoroacetate

2-Methoxy-5-(2-{methyl-[2-(2-phenyl-quinazoline-4-sulfinyl)-ethyl]-amino}-ethyl)-benzenesulfonamide

2-Methoxy-5-{2-[3-(2-phenyl-quinazolin-4-yloxy)-pyrrolidin-1-yl]-ethyl}-benzenesulfonamide

(2S,4S)-2-Methoxy-5-{2-[2-methyl-4-(2-phenyl-quinazolin-4-ylamino)-pyrrolidin-1-yl]-ethyl}-benzenesulfonamide bistriluoroacetate

(2R,4S)-2-Methoxy-5-{2-[2-methyl-4-(2-phenyl-quinazolin-4-ylamino)-pyrrolidin-1-yl]-ethyl}-benzenesulfonamide bistrifluoroacetate

(3S,4R)-2-Methoxy-5-{2-[3-methyl-4-(2-phenyl-quinazolin-4-ylamino)-pyrrolidin-1-yl]-ethyl}-benzenesulfonamide bistrifluoroacetate

2-Benzyl-4-{2-[4-(2-phenylquinazolin-4-yl)piperazin-1-yl]ethyl}phenol

N-(2-Hydroxy-5-{2-[4-(2-phenylquinazolin-4-yl)piperazin-1-yl]ethyl}phenyl)acetamide

1-(2-Methoxy-5-{2-[4-(2-phenylquinazolin-4-yl)piperazin-1-yl]ethyl}phenyl]ethanone

1-{6-[4-(2-Phenylquinazolin-4-yl)piperazin-1-yl]hexanoyl}pyrrolidin-2-one

1-Methanesulfonyl-3-{2-[4-(2-phenylquinazolin-4-yl)piperazin-1-yl]ethyl}imidazolidin-2-one bismaleate

1-(2,2-Dimethylpropionyl)3-{2-[4-(2-phenylquinazolin-4-yl)piperazin-1-yl]ethyl}imidazolidin-2-one

1-{4-[4-(2-Phenylquinazolin-4-yl)piperazin-1-yl]butyryl}piperidin-2-one bis maleate

5-[2-((3-(S)-((2-Phenyl-quinazolin-4-yl)aminomethyl))-pyrrolidin-1-yl)-ethyl]-2-methoxy-benzenesulfonamide hydrochloride

5-[2-((3-(R)-((2-Phenyl-quinazolin-4-yl)aminomethyl))-pyrrolidin-1-yl)-ethyl]-2-methoxy-benzenesulfonamide trifluoroacetate

1-(2-Phenyl-1,3-quinazolin-4-yl)-4-[3-(3-indolyl)propyl]-1,4-piperazine

1-(2-Phenyl-1,3-quinazolin-4-yl)-4-[2-(3-hydroxymethyl-4-methoxyphenyl)ethyl]-1,4-piperazine

1-(2-Phenyl-1,3-quinazolin-4-yl)-4-[2-(3-methanesulfonylaminomethyl-4-methoxyphenyl)ethyl]-1,4-piperazinetrifluoroacetate

1-(2-Phenyl-1,3-quinazolin-4-yl)-4-[2-(3-(1-succinimidoylmethyl)-4-methoxyphenyl)ethyl]-1,4-piperazine, Trifluoroacetic Acid Salt

1-(2-Phenyl-1,3-quinazolin-4-yl)-4-[2-(3-bromo-4-methoxyphenyl)ethyl]-1,4-piperazine, dimaleic acid salt

1-(2-Phenyl-1,3-quinazolin-4-yl)-4-[2-(3-phenylaminocarbonylaminosulfonyl-4-methoxyphenyl)ethyl]-1,4-piperazine

1-(2-Phenyl-1,3-quinazolin-4-yl)-4-[2-(3-(2-tetrahydrofuryl)-4-methoxyphenyl)ethyl]-1,4-piperazine trifluoroaceticacidsalt

2-Methoxy-5-(2-{4-[2-(2-methoxy-phenyl)-quinazolin-4-yl]-piperazin-1-yl}-ethyl)-benzenesulfonamidemaleate salt

2-Methoxy-5-(2-{4-[2-(3-trifluoromethyl-phenyl)-quinazolin-4-yl]-piperazin-1-yl}-ethyl)-benzenesulfonamide

2-Hydroxymethyl-5-(2-{4-[2-(4-nitro-phenyl)-quinazolin-4-yl]-piperazin-1-yl}-ethyl)-benzenesulfonamide

2-Methoxy-5-{2-[4-(2-m-tolyl-quinazolin-4-yl)-piperazin-1-yl]-ethyl}-benzenesulfonamide

2-Methoxy-5-{2-[4-(2-pyridin-4-yl-quinazolin-4-yl)-piperazin-1-yl]-ethyl}-benzenesulfonamide

(2-methoxycarbonylmethylsulfamoyl-4-{2-[4-(2-phenyl-quinazolin-4yl)-piperazin-1-yl]-ethyl}-phenoxy)-acetic acid methyl ester

2-Methoxy-5-{2-[4-(2-phenyl-quinazolin-4-yl)-piperazin-1-yl]-propyl}-benzenesulfonamide

2-methoxy-5-{2-[4-(2-phenyl-quinazolin-4-yl)-piperazin-1-yl]-ethyl}-benzenesulfonamide maleate

2-methoxy-5-{2-[4-(8-chloro-2-phenyl-quinazolin-4-yl)-piperazin-1-yl]-ethyl}-benzenesulfonamide

2-Methoxy-5-{2-[4-(7-chloro-2-phenyl-quinazolin-4-yl)-piperazin-1-yl]-ethyl}-benzenesulfonamide

2-methoxy-5-{2-[4-(2-cyclohexyl-quinazolin-4-yl)-piperazin-1-yl]-ethyl}-benzenesulfonamide maleate

2-methoxy-5-{2-[4-(2-(1H-pyrrol-2-yl)-quinazolin-4-yl)-piperazin-1-yl]-ethyl}-benzenesulfonamide

2-methoxy-5-{2-[4-(2-chloro-quinazolin-4-yl)-piperazin-1-yl]-ethyl}-benzenesulfonamide hydrochloride

2-methoxy-5-{2-[4-(quinazolin-4-yl)-piperazin-1-yl]-ethyl}-benzenesulfonamide

(R) 2-methoxy-5-{2-[3-(2-(3-chloro-4-fluoro-phenyl)-quinazolin-4-yl amino)-pyrrolidin-1-yl]-ethyl}-benzenesulfonamide

2-methoxy-5-{2-[4-(5-chloro-2-phenyl-quinazolin-4-yl)-piperazin-1-yl]-ethyl}-benzenesulfonamide trifluoroacetate

2-methoxy-5-{2-[4-(6-methoxy-2-phenyl-quinazolin-4-yl)-piperazin-1-yl]-ethyl}-benzenesulfonamide trifluoroacetate

3,7-dimethyl-1-{3-[4-(2-phenyl-quinazolin-4-yl)-piperazin-1-yl]-propyl}-3,7-dihydropurine-2,6-dione trifluoroacetate

1-methyl-5-{4-[4-(2-phenyl-quinazolin-4-yl)-piperazin-1-yl]-butylidene}-imidazolidine-2,4-dione

2-Methoxy-5-{3-[4-(2-phenyl-quinzolin-4-yl)-piperazin-1-yl]-propyl}-benzenesulfonamide

2-Methoxy-N-methyl-5-{2-[4-(2-phenyl-quinazolin-4-yl)-piperazin-1-yl]-ethyl}-benzenesulfonamide bismaleate

2-Methoxy-N,N-dimethyl-5-{2-[4-(2-phenyl-quinazolin-4-yl)-piperazin-1-yl]-ethyl}-benzenesulfonamide bismaleate

N-Acetyl-2-methoxy-5-{2-[4-(2-phenyl-quinazolin-4-yl)-piperazin-1-yl]-ethyl}-benzenesulfonamide

N-Acetyl-2-methoxy-N-methyl-5-{2-[4-(2-phenyl-quinazolin-4-yl)-piperazin-1-yl]-ethyl}-benzenesulfonamide bistrifluoroacetate

2-{3-[4-(2-phenyl-quinazolin-4-yl)-piperazin-1-yl}-propyl}-isoindole-1,3 dione

3-{2-[4-(2-phenyl-quinazolin-4-yl)-piperazin-1-yl]-ethoxy}-benzamide

1,3-Dimethyl-9-{2-[4-(2-phenyl-quinazolin-4-yl)-piperazin-1-yl]-ethyl}-3,9-dihydro-purine-2,6-dione bistrifluoroacetate

4-{4-[2-(7-Methoxy-1,2,3,4-tetrahydro-naphthalen-2-yl)-ethyl]-piperazin-1-yl}-2-phenyl-quinazoline

4-{4-[2-(6-Methoxy-1,2,3,4-tetrahydro-naphthalen-2-yl)-ethyl]-piperazin-1-yl}-2-phenyl-quinazoline bistrifluoroacetate

2,2,3,3,-Tetramethyl-cyclopropanecarboxylic acid {3-[4-(2-phenyl-quinazolin-4-yl)-piperazin-1-yl}-propyl}-amide maleate

Tetrahydro-furan-2-carboxylic acid {2-[4-(2-phenyl-quinazolin-4-yl)-piperazin-1-yl]-ethyl}-amide bistrifluoroacetate

4-[4-(3,3-Diphenyl-propyl)-piperazin-1-yl]-2-phenyl-quinazoline

4-[4-(2-Naphthalen-1-yl-ethyl)-piperazin-1-yl}-2-phenyl-quinazoline

2-(2-methoxy-5-{2-[4-(2-phenyl-quinazolin-4-yl)-piperazin-1-yl]ethyl}-benzenesulfonylamino)-acetamide

4-(4-Benzyl-piperazin-1-yl)-2-phenyl-quinazoline

{1-Methyl-5-[4-(2-phenyl-quinazolin-4-yl)-piperazin-1-yl-methyl]-1H-pyrrol-2-yl}-acetic acid methyl ester

N-Methyl-2-{1-methyl-5-[4-(2-phenyl-quinazolin-4-yl)-piperazin-1-yl-methyl]-1H-pyrrol-2-yl]acetamide

N-(3-{1-hydroxy-2-[4-(2-phenyl-quinazoline-4-yl)-piperazin-1-yl]-ethyl}-phenyl)-methansulfonamide bis-maleic acid salt

2-Methoxy-5-{2-[4-(2-phenyl-quinazoline-4-yl)-piperazin-1-yl]-ethyl}-benzoic acid methyl ester

2-Methoxy-N-methyl-5-{2-[4-(2-phenyl-quinazolin-4-yl)-piperazin-1-yl]-ethyl}-benzamide bis-maleic acid salt

2-Methoxy-5--{2-[4-(2-phenyl-quinazolin-4-yl)-piperazin-1-yl]-ethyl}-benzamide bis-maleic acid salt

4-{2-[4-(2-Phenyl-quinazolin-4-yl)-piperazin-1-yl]-ethyl}benzamide

4-{4-[4,4-Bis-(4-fluoro-phenyl)-butyl]-piperazin-1-yl}-2-phenyl-quinazoline

5-{1-hydroxy-2-[4-(2-Phenyl-quinazolin-4-yl)-piperazin-1-yl}-2-methoxy-benzamide4-(3-phenyl piperazin-1-yl)-2-phenyl-quinazoline

5-{2-[2-phenyl-4-(2-phenyl-quinazolin-4-yl)-piperazin-1-yl}-ethyl}-2-methoxy-benzenesulfonamide bistrifluoroacetate

2-(2-phenyl-quinazolin-4yl)-2,3,4,6,7,11b-hexahydro-1H-pyrazino[2,1-alisoquinoline

5-{2-[2,2-dimethyl-4-(2-phenyl-quinazolin-4-yl)-piperazin-1-yl}-ethyl}-2-methoxy-benzenesulfonamide dimaleate sesquihydrate

5-{2-[1-(2-Phenyl-quinazolin-4yl)-piperidin-1-ylamino]-methyl}-2-methoxy-benzenesulfonamide bistrifluoroacetate dihydrate

2-Methoxy-5-{2-[8-(2-phenyl-quinazolin-4-yl)-3,8-diaza-bicyclo[3.2.1]oct-3-yl]-ethyl}-benzenesulfonamide bistrifluoroacetate monohydrate.

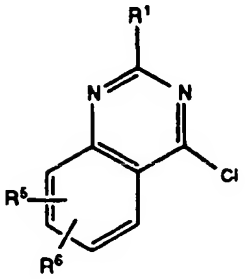
9. A pharmaceutical composition comprising a quinazoline compound of Claim 1 and a pharmaceutically acceptable diluent or carrier.

10. A method for the treatment of benign prostatic hyperplasia which comprises administering to a patient in need of such the pharmaceutical composition of Claim 9

11. The method of Claim **11**, wherein the pharmaceutical composition thereof is administered to a patient along with a therapeutic agent active against the 5-α reductase enzyme.

12. A process for the preparation of the quinazoline compounds of Claim 1, the process comprising:

Reacting a compound of formula (1a):



with a compound of formula (2b):

$$HR^2—(R^3)_n—R^4$$

(2b)

to yield a compound of formula (I).

The Patent Office

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Application No: GB 9423635.3
Claims searched: 1-12

Examiner: Peter Davey
Date of search: 22 January 1996

Patents Act 1977
Search Report under Section 17

Databases searched:

UK Patent Office collections, including GB, EP, WO & US patent specifications, in:

UK Cl (Ed.O): C2C (CSF, CZB, CWE, CNF)

Int Cl (Ed.6): C07D

Other: Online: WPI

Documents considered to be relevant:

Category	Identity of document and relevant passage		Relevant to claims
X	GB1390014	(KONINKLIJKE), see eg. Exs. VII,VIII,IX	1 at least
X	GB1302709	(SANDOZ), see eg. Exs. 3,6,12	1 at least
X	GB1297595	(BRISTOL-MYERS),see eg. Procedures 2-5	1 at least
X	GB1199768	(PFIZER), see eg. Tables	1 at least
X	GB1182507	(SANDOZ), see eg. Tables	1 at least

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art.
Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention.
&	Member of the same patent family	E	Patent document published on or after, but with priority date earlier than, the filing date of this application.